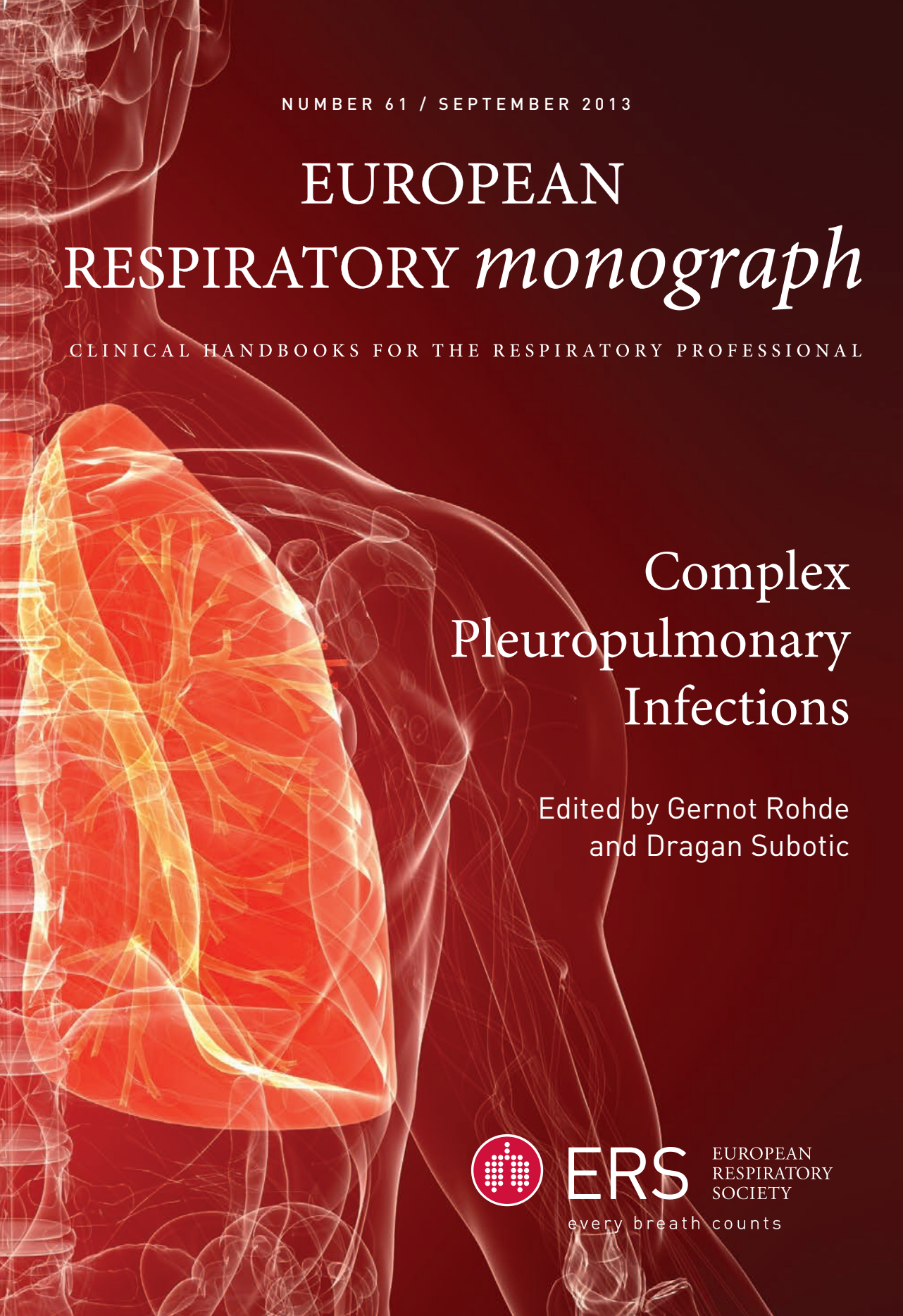
NUMBER 61 / SEPTEMBER 2013

EUROPEAN RESPIRATORY *monograph*

CLINICAL HANDBOOKS FOR THE RESPIRATORY PROFESSIONAL



Complex Pleuropulmonary Infections

Edited by Gernot Rohde and Dragan Subotic

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

European Respiratory Monograph 61, September 2013

Complex Pleuropulmonary Infections

Edited by
Gernot Rohde and Dragan Subotic

Editor in Chief
Tobias Welte

Published by European Respiratory Society ©2013
September 2013
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674
Printed by Page Bros Ltd, Norwich, UK

Managing Editors: Rachel White and Catherine Pumphrey
European Respiratory Society
442 Glossop Road, Sheffield,
S10 2PX, UK
Tel: 44 114 2672860
E-mail: Monograph@ersj.org.uk

All material is copyright to European Respiratory Society. It may not be reproduced in any way including electronic means without the express permission of the company.

Statements in the volume reflect the views of the authors, and not necessarily those of the European Respiratory Society, editors or publishers.

THOMSON REUTERS BOOK CITATION INDEX INDEXED

MIX Paper from responsible sources FSC® C023114 FSC www.fsc.org

This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

Contents

Number 61 September 2013

Preface v

Guest Editors vii

Introduction ix

1. Antibiotic prophylaxis in lung resection surgery 1
Marco Alifano, Antoine Rabbat, Antoine Tesnière and Nicolas Roche

2. Medical treatment of pulmonary tuberculosis 11
Giovanni Sotgiu, Rosella Centis, Lia D'Ambrosio and Giovanni Battista Migliori

3. Surgical treatment of pulmonary tuberculosis 20
Piotr Yablonski, Ioan Cordos, Eugeny Sokolovich, Nicolas Schönfeld, Joachim Pfannschmidt and Igor Vasilyev

4. Fungal pulmonary infections: the conservative approach 37
Matteo Bassetti and Elda Righi

5. Surgical management of thoracic aspergillosis 50
Gilbert Massard, Anne Olland, Nicola Santelmo and Pierre-Emmanuel Falcoz

6. Surgical treatment of invasive aspergillosis 58
Adelheid End, Birgit Willinger and Oliver A. Cornely

7. Actinomycosis of the lung and pleura 66
Martin Kolditz and Adelheid End

8. Abscess of the lung: current therapeutic options 81
Kalliopi Athanassiadi, Radoslav Jaković and Nikolaos Siafakas

9. Surgical treatment of bronchiectasis 90
Dragan Subotic and Didier Lardinois

10. Hydatid disease of the lungs 107
Danail Petrov and Kalliopi Athanassiadi

11. Mediastinitis: causes, management and outcomes 122
Stefano Elia, Adelheid End, Emilio Canalis, Hartmut Lode, Alessandra Vittoria Granai and Giuseppe Petrella

12. Surgical management of pleural empyema 141
Michel Gonzalez, Hans-Beat Ris and Danail Petrov

13. Pleural empyema in children 153
Jeroen M.H. Hendriks, Martine Sabbe, Jan Verhaegen, Patrick Lauwers, Stijn Verhulst and Paul E.Y. Van Schil

14. Lung resection in the presence of infection and after pleural empyema 162
Dragan Subotic and Francoise Le Pimpec Barthes

15. Dealing with infection after thoracic surgical procedures 171
Emilio Canalis, Danail Petrov and Antoni Torres

CME credit application form 181

C O P E COMMITTEE ON PUBLICATION ETHICS

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics.

Preface

Since the beginning of the last century, respiratory medicine has evolved as a specialism from the study of respiratory physiology. Consequently, for over a hundred years, obstructive airway diseases such as asthma and chronic obstructive pulmonary disease have been an important focus of chest physicians. Although these diseases are still of continued importance, the spectrum of pulmonary diseases now studied has been greatly expanded and includes thoracic oncology, allergology, pulmonary infections, sleep medicine and intensive care medicine. In addition, the collaborations between paediatricians and pulmonologists and between surgeons and pneumologists have become more and more important.

In the preface to the previous issue of the *European Respiratory Monograph* (*ERM*), whose topic was bronchial infections, I pointed out that the 21st century will one day be described as the century of infectious diseases. The economic crisis has contributed to a deterioration of the social and hygiene conditions in many parts of the world, creating a breeding ground for the spread of infectious diseases. Antibiotic overconsumption has led to an exponential growth of resistant organisms. The globalisation of the economy has contributed to the spread of these resistant infectious agents, while the development of new antibiotics has not kept pace with the development of resistance. Therefore, surgical measures again play an essential role in the treatment of infectious pathogens, as was the case in the era of tuberculosis before World War II.

The present issue of the *ERM* summarises the most important infectious diseases that need a common therapeutic approach between thoracic surgeons and pneumologists. I want to congratulate the Guest Editors, Gernot Rohde and Dragan Subotic, for their tremendous work in setting up this excellent trendsetting *ERM*, which should be of interest to pneumologists, infectious disease specialists and thoracic surgeons alike. I hope this book will stimulate joint research, leading to better understanding and more successful therapy, and I am convinced that readers will find this *ERM* useful for their daily work.

Eur Respir Monogr 2013; 61: v. Copyright ERS 2013. DOI: 10.1183/1025448x.10007713. Print ISBN: 978-1-84984-036-1. Online ISBN: 978-1-84984-037-8. Print ISSN: 1025-448x. Online ISSN: 2075-6674.

Guest Editors

Gernot Rohde

Gernot Rohde is Associate Professor of Respiratory Medicine at the Maastricht University Medical Center (Maastricht, the Netherlands), as well as the chairman of the executive board of CAPNETZ (Competence Network for Community-Acquired Pneumonia) and a member of the executive board of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium). Currently he is External Activities Director of the European Respiratory Society (ERS) and HERMES (Harmonised Education in Respiratory Medicine for European Specialists) Director Elect.

Gernot Rohde graduated from medical school in 1998 and was recognised as a specialist in internal medicine in 2004. He completed an ERS fellowship at the Imperial College London (London, UK) in 2005, and finished his specialisation as a pulmonologist in 2006 in Germany. His fields of scientific interest include respiratory infections in asthma and chronic obstructive pulmonary disease (COPD) with a focus on viral pathogens, new detection methods for respiratory viruses (real-time PCR), the role of emerging respiratory viruses, inflammation caused by and innate immune responses towards respiratory viruses, community-acquired pneumonia, and detection of latent tuberculosis. He has published more than 75 scientific articles listed in PubMed. He is associate editor of *PLoS One*, *Breathe* and *The Clinical Respiratory Journal*.

Dragan Subotic

Dragan Subotic is a professor of surgery at the University of Belgrade School of Medicine and director of the Clinic for Thoracic Surgery, Clinical Center of Serbia, in Belgrade. He is an active member of the European Association for Cardiothoracic Surgery (EACTS), being a member of the thoracic domain in 2008–2011, and currently chairing the working group for pleuropulmonary infections of this association. Since 1999, Dragan Subotic has been actively participating within the surgical assembly of the ERS. The focus of his activities is to maintain and promote multidisciplinary activity of surgical and other assemblies, mostly in the form of joint scientific events during the annual congresses and through external educational courses.

The dominant field of professional activity of Dragan Subotic is general thoracic surgery, including diagnostics and treatment of malignant and nonmalignant diseases of the lungs, pleura, mediastinum and chest wall.

Eur Respir Monogr 2013; 61: vii.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10007513
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Introduction

Gernot Rohde[*] *and Dragan Subotic*[#]

[*]*Dept of Respiratory Medicine, Maastricht University Medical Center, Maastricht, The Netherlands.* [#]*Clinic for Thoracic Surgery, Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia.*

Correspondence: G. Rohde, Dept of Respiratory Medicine, Maastricht University Medical Center, P. Debyelaan 25, 6202AZ Maastricht, The Netherlands. Email: g.rohde@mumc.nl

As cause of death, lower respiratory tract infections rank first in lower-income, third in lower-middle-income, fifth in upper-middle-income and sixth in high-income countries, accounting for 3.2 million deaths in 2011 worldwide, according to figures from the World Health Organization [1]. Lower respiratory tract infections cover a broad spectrum, from acute bronchitis to severe pneumonia and their complications. Many aspects have recently been covered in the *European Respiratory Monograph* (*ERM*) entitled "The Spectrum of Bronchial Infection" [2]. The topics of the current issue of the *ERM* extend the field to infections of the lungs, pleura and mediastinum and try to integrate conservative and surgical treatment, which plays a more important role in this field as compared to infections of the airway compartment.

The role of surgery in the treatment of pleuropulmonary infections mostly depends on the possibilities of medical treatment. Tuberculosis (TB) is a good example to illustrate the trend that surgical treatment has followed, from collapse therapy before the era of potent anti-TB drugs, through elective lung-sparing resections for localised forms of disease, to salvage surgery for multidrug-resistant TB, sometimes as a medical urgency [3]. Most forms of TB are treated by antimicrobial chemotherapy and the most recent updates to this treatment are therefore also covered in this issue.

One of the specific characteristics of lung infections is a radiographic evolution with a wide variety of initial pleuropulmonary presentations, sometimes mimicking the underlying disease. This often imposes the need for additional diagnostic procedures (*e.g.* bronchoscopy, thoracocentesis, chest tube insertion or thoracoscopy) before the decision on treatment. These procedures should be dealt with only in adequately equipped institutions with the possibility of permanent radiographic control of patients. Furthermore, some of these infections, like aspergillosis or bronchiectasis, may require surgery without the possibility of thorough assessment of a patient. In these cases, urgent temporary procedures, like bronchial artery embolisation, may sometimes be necessary.

Bilateral lesions, for example as found in patients with bronchiectasis, represent a specific challenge for the surgeon. Therefore, a thorough knowledge of the conservative treatment options is mandatory. Attitudes have moved from surgery exclusively for unilateral disease, to bilateral operations in selected patients, sometimes with the use of modern video-assisted procedures [4].

The progress in the field of video-assisted procedures has greatly influenced the treatment of pleural empyema, making early disease stages amenable to efficient treatment in a less invasive way. This results in an indication for open surgery only in advanced stages [5]. As management is different for children and adults, separate chapters have been included for these two groups.

Some of these pleuropulmonary infections also affect extrathoracic organs, for example in hydatid disease. In this situation, a combined operative approach to expose thoracic and abdominal cavities is necessary, either for one- or two-stage procedures.

Eur Respir Monogr 2013; 61: ix–x. Copyright ERS 2013. DOI: 10.1183/1025448x.10007613. Print ISBN: 978-1-84984-036-1. Online ISBN: 978-1-84984-037-8. Print ISSN: 1025-448x. Online ISSN: 2075-6674.

Taken together, complex pleuropulmonary infections require an experienced team, familiar with a broad spectrum of pulmonary diseases and also capable of preventing and dealing with post-operative complications in patients in whom major surgery is anticipated due to the presence of the existing or previous infection.

References

1. World Health Organization. The Top 10 Causes of Death. The 10 leading causes of death by income group (2011). Factsheet available at http://www.who.int/mediacentre/factsheets/fs310/en/index1.html
2. Blasi F, Miravitlles M, eds. The Spectrum of Bronchial Infection. *Eur Respir Monogr* 2013; 60.
3. Furak J, Trojan I, Szöke T, *et al.* Surgical intervention for pulmonary tuberculosis: analysis of indications and perioperative data relating to diagnostic and therapeutic resections. *Eur J Cardiothorac Surg* 2001; 20: 722–727.
4. Schneiter D, Meyer N, Lardinois D, *et al.* Surgery for non-localized bronchiectasis. *Br J Surg* 2005; 92: 836–839.
5. Wurnig PN, Wittmer V, Pridun NS, *et al.* Video-assisted thoracic surgery for pleural empyema. *Ann Thorac Surg* 2006; 81: 309–313.

Chapter 1

Antibiotic prophylaxis in lung resection surgery

Marco Alifano[*], *Antoine Rabbat*[#], *Antoine Tesnière*[¶] *and Nicolas Roche*[#]

SUMMARY: Post-operative pneumoniae are a major source of post-operative morbidity and mortality in patients undergoing lung resection surgery. Empyema is another severe complication, most frequently related to bronchopleural fistula, although empyema without fistula exists in pneumonectomy patients. Risk factors for infectious post-operative complications include smoking history, underlying chronic obstructive pulmonary disease, other comorbidities including lung cancer, impaired nutritional status and extra-thoracic chronic diseases. The extent of resection and peri-operative care also play a role, as well as the presence of pre-existing airway colonisation. The most frequent pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and Gram-negative pathogens. Altogether, the relatively small number of randomised controlled trials available provides convincing evidence supporting the use of antibiotic prophylaxis in patients undergoing lung surgery. The evidence is strong for prevention of wound infection, but more limited for empyema and post-operative pneumonia. First- and second- generation cephalosporins have been the most extensively used prophylactic antibiotics. Amoxicillin–clavulanate has also been shown to be effective. The optimal duration of prophylactic antibiotic treatment has not been extensively studied. Similarly, how antibiotic prophylaxis could be tailored to specific populations or risk factors is currently unknown.

[*]Thoracic Surgery Dept, [#]Respiratory and Intensive Care Medicine Dept, and [¶]Anesthesia and Surgical Intensive Care Dept, Cochin-Broca-Hôtel-Dieu Hospital, Assistance Publique Hôpitaux de Paris, Paris Descartes University, Paris, France.

Correspondence: N. Roche, Pneumologie, Groupe Hospitalier Cochin-Broca Hôtel-Dieu, AP-HP, Site Val de Grâce, Hôpital d'Instruction des Armées du Val de Grâce, 74 boulevard de Port-Royal, 75230 Paris cedex 05, France.
Email: nicolas.roche@htd.aphp.fr

Eur Respir Monogr 2013; 61: 1–10.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040112
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Patients undergoing lung resection surgery are at a high risk of complications such as post-operative pneumonia (POP) and empyema. This chapter will focus on the prophylactic antibiotics that are available for these patients. The main purpose of peri-operative antibiotic therapy in lung resection patients is to reduce the incidence of POP, which can be considered as a surgical site infection when it occurs within 30 days of surgery. The decision to administer antibiotic prophylaxis should rely on several considerations: the incidence of post-operative infections, the risk of poor outcome, the presence of specific risk factors, and the risks and outcomes of antibiotic-related adverse events. Outcomes of interest when assessing the utility of antibiotic prophylaxis include not only the frequency of target events (*i.e.* infections) or unwanted events (*e.g.* allergy and renal function impairment) but also mortality, intensive care unit (ICU) and hospital length of stay, risk of delayed infection and costs.

Infection represents the most frequent post-operative complication following lung resection, and POP is a major source of post-operative mortality. Of all surgical procedures, lung surgery by itself is one of the major risk factors for POP [1]. Risk factors for infectious post-operative complications can be categorised into two groups: patient-related risk factors and surgery-related risk factors. Patient-related risk factors for POP include some demographic characteristics (older age and male sex), impaired pre-operative lung function (most frequently related to chronic obstructive pulmonary disease (COPD)), persistent smoking, poor nutritional status and pre-operative bacterial colonisation. Some risk factors are related to surgery (extent of resection, with an increased risk following pneumonectomy, right-sized surgery and duration of surgery), post-operative management (mechanical ventilation, pain control strategy and transfusion) [2], and occurrence of other pulmonary complications (especially atelectasis and complications requiring mechanical ventilation). Only a few of these risk factors are modifiable before surgery, *e.g.* smoking and nutritional status [3].

Thus, prophylactic antibiotics to prevent the occurrence of respiratory infections could well be of interest to decrease post-operative morbidity and mortality.

In this chapter, we will first review in more detail the incidence, outcome and risk factors of the various types of post-operative respiratory infections. Following this, we will analyse studies reporting the efficacy and utility of antibiotic prophylaxis, giving consideration to the influence of the extent of lung resection on the possible benefits this approach could provide.

Post-operative infectious complications

Incidence

POP

Retrospective and prospective studies provide extremely variable results in terms of incidence of POP after lung resection, with values ranging from 2% to 40% (table 1) [3–7]. For instance, DÍAZ-RAVETLLAT *et al.* [3] prospectively studied 604 patients undergoing surgery for bronchogenic carcinoma between January 1999 and June 2004 and found a rather low (22 cases (3.6%)) incidence of POP. In a more recent retrospective cohort study performed by LEE *et al.* [2] to identify risk factors of POP following surgical resection for lung cancer, the proportion of patients who developed POP was almost two times higher (26 (6.2%) out of 417) [2]. In this study [2], the median time between surgery and diagnosis of POP was 4 days (range 1–19 days). Empyema developed in three patients, of whom two had both POP and empyema. The study by SCHUSSLER *et al.* [5] included patients with more severe comorbidities and found a 25% incidence of POP (42 out of 168). Finally, in a prospective study including 129 patients undergoing pneumonectomy, the overall hospital mortality rate was 10.8% and complications occurred in 42.6% , with bacterial pneumonia being the most prevalent complication in 29 (22%) out of 129 patients [5].

Such variability of POP incidence between studies probably reflects differences in: 1) criteria used to define POP; 2) diagnostic procedures used to identify the criteria; 3) the populations studied; 4) surgical procedures used; and 5) peri-operative management, including prophylactic antibiotics. The post-operative documentation of involved pathogenic micro-organisms is also problematic. Thus, between 29% and 50% of post-operative pulmonary infections remain undocumented.

Table 1. Variability of post-operative pneumonia incidence and mortality in patients undergoing lung resection summarising data from three studies addressing these two criteria

First author [ref.]	Subjects n	Incidence %	Mortality %
DÍAZ-RAVETLLAT [3]	604	3.6	32
LEE [2]	417	6.2	27
SCHUSSLER [5]	168	25	19

Other types of post-operative respiratory infections

Empyema is a less frequent but severe post-operative infection that may complicate any

kind of pulmonary surgery. Empyema is defined as the presence of purulent material in the pleural space. It is frequently related to a bronchopleural fistula (BPF) involving the stump of the main bronchus or of a lobar or segmental bronchus; air leaks may also originate from more peripheral bronchi, as well as from bronchoalveolar fistulae in the remaining lung. Empyema may also occur without BPF and, in this case, usually relates to pleural space bacterial contamination occurring peri-operatively. BPF has been reported with an incidence of 1.5–28% after pulmonary surgery [8]. Incidence after pulmonary resection for lung cancer is reported to be between 4.5% and 20% after pneumonectomy and 0.5% after lobectomy [9].

Outcome

POP

Despite advances in surgical techniques, anaesthesia and peri-operative care, nosocomial pneumonia after thoracic surgery is associated with high rates of respiratory failure and longer ICU and hospital stay [10]. POP is one of the main causes of post-operative mortality, which ranges from 22% to 67% when this complication occurs [11].

In the Eole study [12], a multicentre, prospective study performed to evaluate the predictive factors of mortality due to POP (which was strictly defined), the overall mortality among the 556 cases of POP was 23% (126 patients) [12]. In their study, SCHUSSLER *et al.* [5] used a similar definition of POP, and found a death rate of 19% among the 42 patients who developed POP *versus* 2.3% in patients who did not ($p=0.0012$). Patients with POP required noninvasive ventilation (NIV) or re-intubation more frequently than patients who did not develop POP (45.2% *versus* 5.6% and 23.8% *versus* 4.0%, respectively). POP was associated with longer ICU and hospital stay of 7 (5–13) days *versus* 3 (2–5) days and 16 (11–22) days *versus* 9 (7–12) days, respectively. All these differences between patients with *versus* without POP were highly significant. In the study by DÍAZ-RAVETLLAT *et al.* [3], the overall in-hospital mortality rate was 5.3% in patients who underwent resection of bronchogenic carcinoma. Among patients with POP, in-hospital mortality was 31.8% [3]. In the prospective cohort study performed by BELDA *et al.* [13], patients with post-operative respiratory infections had a significantly higher length of respiratory intensive and intermediate care unit and hospital stay when compared with those without a post-operative infectious complication. Only POP was associated with a significantly higher mortality (33% *versus* 3%). In the retrospective cohort study performed by LEE *et al.* [2], patients with POP frequently required mechanical ventilation (42.3%) and had a higher rate of acute respiratory distress syndrome (34.6%) and in-hospital mortality (27%) [2]. Interestingly, NIV may improve short-term outcomes in patients with acute respiratory failure following lung resection surgery [14]. In an observational prospective cohort survey, LEFEBVRE *et al.* [15] confirmed the feasibility and efficacy of NIV in both hypercapnic and hypoxic acute respiratory failure following lung resection. In this study [15], univariate analysis found an association between POP and NIV failure: POP was present in 92.3% of patients with NIV failure *versus* 38.1% of patients with NIV success ($p=0.0016$).

The impact of respiratory post-operative infections on long-term survival after lung resection for cancer has rarely been studied. YAMADA *et al.* [7] performed a retrospective chart review including 626 patients who underwent lung cancer surgery between 1996 and 2005. POP occurred in 40 patients (6.4%) and was more frequent in patients with COPD (14.3% *versus* 3.6%; $p<0.0001$). Patients with POP had a significantly worse overall survival rate than those who did not have POP ($p=0.0004$).

Empyema

Empyema is also a life-threatening condition with a mortality rate of ~40% in post-pneumonectomy patients. The presence of BPF obviously increases the morbidity and mortality of empyema by providing a source of continuous contamination of the pleural space and promoting aspiration of infected pleural fluid. Among patients with BPF and empyema following thoracic surgery, mortality rates of 18–50% have been reported [16]. A particularly poor prognosis

exists for BPF requiring mechanical ventilation, where air leaks can reach 500 mL per breath [17]. Right pneumonectomy complicated by BPF and empyema is associated with a high mortality. In cases without BPF, more conservative treatment may be proposed, avoiding aggressive surgical treatment; in such cases, lower mortality rates have been reported [18].

Risk factors

Many patients undergoing major lung resections carry risk factors of nosocomial pneumonia, including smoking history, coexistent chronic bronchitis or COPD, neoplastic disease, extrathoracic comorbidities and a poor nutritional status. Finally, surgery involves the respiratory system itself. Tracheobronchitis and purulent sputum retention are frequent and may lead to atelectasia and pneumonia.

Airway colonisation

Airway colonisation (AWC) is supposed to be an essential first step in the pathogenesis of nosocomial pneumonia and acute respiratory distress syndrome [19]. Patients undergoing lung resection surgery (mostly for bronchial carcinoma) have many factors predisposing them to bronchial colonisation. AWC is supposed to facilitate the development of POP when secretion clearance and cough reflex are impaired. Under immunosuppressive conditions, such as surgery, cancer or impaired nutritional status, the ability of the respiratory mucosal surface to bind micro-organisms increases, which in turn increases the risk of infection. Lung infection would thus be the result of a decrease in the host's cellular and humoral defences and/or of the presence of bacterial inoculum in sufficient quantity or with a sufficient virulence to overwhelm local and general defence systems.

Several studies have analysed peri-operative bronchial colonisation and related outcome. WANSBROUGH-JONES *et al.* [20] investigated 75 patients undergoing pulmonary or pleural resection by performing cultures from samples obtained by pre-operative bronchoalveolar lavage. They found pathogenic micro-organisms in 23% of cases, *Haemophilus influenzae* being the most frequent bacteria. Of the 75 patients, 11% developed post-operative infectious respiratory complications, of which 42% was in those patients whose lavage culture was positive for bacterial pathogens and 4.8% in those with negative cultures. In 2002, a prospective study of respiratory infections after lung cancer resection was performed by SOK *et al.* [21], who studied samples of sputum obtained 3 days before, during and 3 days after surgery. In 75% of cases, micro-organisms involved in lung infections were Gram-negative bacilli and *Candida albicans*. These were isolated in 18%, 13% and 63% of sputum samples taken pre-, intra- and post-operatively, respectively. These authors also found a strong association between the pathogens found in the sputum obtained 3 days after the operation and those found when lung infection developed. In a prospective study based on protected specimen brush in 41 patients with cancer, IOANAS *et al.* [22] found that 41% presented with bacterial colonisation, mainly by potentially pathogenic micro-organisms (PPMs) (36%). In multivariate analysis, two factors were independently associated with AWC: body mass index >25 kg·m^{-2} and proximal location of the tumour. However, in univariate analysis, there was no correlation between AWC and post-operative infection. The prospective study by BELDA *et al.* [13] was based on bilateral protected specimen brush before thoracotomy. AWC was present in 65 of 78 patients (83%), involving PPMs in 36% and non-PPMs in 72% of patients. A positive correlation between AWC and post-operative pulmonary complications was found in multivariate analysis. In the observational prospective study by SCHUSSLER *et al.* [5], in 168 patients with resectable lung cancer, bilateral bronchoscopic aspirates allowed the isolation of AWC in 22.8% of patients. The bacterial agents were mainly *H. influenzae* (61%), *Streptococcus pneumoniae* (29%) and polymicrobial (29%). Multivariate analysis again found a positive correlation between AWC and post-operative pulmonary complications. Recently, DANCEWICZ *et al.* [23] reported AWC in 59% of 44 patients, but none of these developed post-operative pulmonary infections. Finally, a retrospective evaluation of 626 patients who all had pre- and post-operative sputum samples or aspirates was published in 2010 by YAMADA *et al.* [7]. AWC was

present in 10.5% of non-COPD patients and in 20% in COPD patients. Again, multivariate analysis showed a positive association between AWC and post-operative pulmonary complications.

Risk factors for BPF and empyema

Empyema and POP share many risk factors including advanced age, high number of comorbidities, COPD and bacterial AWC. Some risk factors for BPF and empyema are probably more specific: their incidence is highest after right pneumonectomy and right lower lobectomy and in the case of bronchial anastomosis. Increased incidence of BPF is also reported in the case of incomplete tumour resection, steroid use and pre-operative radiotherapy [24]. Post-operative mechanical ventilation is also a significant independent risk factor [25].

Involved pathogens

When documentation is obtained, encountered pathogenic bacteria are, in most instances, those classically reported for early hospital-acquired pneumonia [20]: *H. influenzae* (3–66%), *S. pneumoniae* (3–29%) and *Staphylococcus aureus* (8–19%). A polymicrobial aetiology is found in 15–33% of patients, and *Enterobacter* and *Pseudomonas* species are responsible for <10% of cases. In the study by SCHUSSLER *et al.* [5], pathogenic bacteria were, in most cases, those classically reported for early hospital-acquired pneumonia: *H. influenzae* (41.7%), *S. pneumoniae* (25%) and other Streptococci (12.5%). Enterobacteriaceae and *Pseudomonas* spp. were responsible for 21.2% and 25% of cases, respectively. A polymicrobial aetiology was recognised in 33.3% of patients. Among *S. pneumoniae* strains, 22.2% had a decreased sensitivity to penicillin G while 26% of *Haemophilus* strains were β-lactamase positive.

BERNARD *et al.* [26] also found that *Streptococcus* spp. and *H. influenzae* were responsible for 50% of all POP, whereas Gram-negative pathogens (other than *Haemophilus* spp.) accounted for 31% of pneumonias. In the study by SOK *et al.* [21], slightly different results were found. Gram-negative pathogens (other than *Haemophilus* spp.) were responsible for 71% of post-operative pulmonary complications and Streptococcus species were found in only 10% of cases. In this study, a single-dose cefuroxime was utilised as pre-operative antibioprophylaxis, but 44% of patients had been treated with the same drug for 1–6 days pre-operatively, with a possible impact on their bacterial flora.

Antibiotic prophylaxis

Efficacy of antibiotic prophylaxis in lung resection: results of clinical trials

The usefulness of antibiotic prophylaxis in lung resection has been investigated in several randomised trials, beginning in the late 1970s, with initially conflicting results. A randomised, prospective double-blind study performed in 1977 by KVALE *et al.* [27] compared placebo with cefazolin 500 mg intramuscular, starting upon arrival in the operating room, followed by cefazolin 500 mg *i.m.* every 6 h, then oral cephalexin 500 mg when oral intake was restarted, for a total of 5 days altogether. Among the 34 patients randomised in the placebo group, 17 infections were recorded (50%), compared with eight in the 43 (19%) patients of the antibiotic group ($p=0.005$). With respect to the site of infection, 14 thoracic infections occurred in the placebo group (41%) compared with two (4.7%) in the antibiotic group ($p=0.0002$). No correlation was found between the occurrence of infection and the extent of pulmonary resection. Furthermore, the authors failed to identify specific risk factors of occurrence of post-operative infections: in particular, history of smoking, presence of chronic bronchitis, spirometric abnormalities and obesity were not related to the occurrence of infection. Following this initial trial, peri-operative cephalosporin prophylaxis in thoracic surgery became common practice.

However, two subsequent randomised trials did not confirm these initial findings. TRUESDALE *et al.* [28] performed a prospective, double-blind trial comparing placebo with cephaloxin 1 g *i.m.* in the operating room prior to pulmonary resection, followed by 2 g intravenous every 6 h

for a total of 48 h. The incidence of post-operative infections was the same in the two study arms: five (17.8%) out of 28 patients in the cephalosporin group and (17.2%) five out of 29 in the placebo group. Of the five infection-related deaths, three occurred in the placebo group and two in the cephalosporin arm. Most other outcomes were similar in both arms, including white blood cell count, fever, duration of hospitalisation, hypersensitivity reactions or abnormal liver functions. Phlebitis and abnormal renal function occurred more often in the cephalosporin group. In the subsequent study by CAMERON *et al.* [29], no difference in terms of post-operative infections was observed between the 88 patients receiving 2 g *i.v.* cephalotin prior to and 6 h after pulmonary surgery as compared to placebo (n=83). Specifically, there was no difference in the number of post-operative days with fever, number of post-operative septic complications and length of post-operative stay. It is of note that, in this study, topical antibiotics were used in the pleural cavity and wound of all patients. Unfortunately, the authors did not provide the number of wound infections in each group, but they underlined that, when post-operative infectious complications developed in the antibiotic group, they were often secondary to Gram-negative organisms resistant to cephalotin.

After these initially conflicting studies hampered by limited numbers of evaluated patients and heterogeneity in evaluation criteria and their definition, subsequent trials provided convincing evidence of the superiority of antibiotic prophylaxis over placebo in lowering the incidence of post-operative infectious complications. In these studies, the different kinds of post-operative infections were taken into account and more attention was paid to pulmonary infections.

In the Canadian study by ILVES *et al.* [30], 211 patients undergoing oesophageal or pulmonary surgery were randomised to cephalotin 2 g *i.v.* in the operating room followed by 2 g *i.v.* 4 h later, *versus* placebo. A significant decrease in wound infections was observed: 22 (23.7%) out of 93 patients in the placebo group *versus* seven (5.9%) out of 118 in the cephalotin group. POP and empyema occurred numerically less frequently among patients undergoing antibiotic prophylaxis, but statistical significance was not achieved.

One year later, in 1982, FRIMODT-MØLLER *et al.* [31] compared placebo with penicillin G (5 million IU *i.v.* prior to surgery and thereafter every 6 h for a total of five doses). They could evaluate 92 out of 101 included patients, 45 receiving penicillin and 47 placebo. They found that penicillin had no effect on the occurrence of lower respiratory tract infections (19 out of 47 *versus* 15 out of 45), empyema (two in both groups) or fever of unknown origin, whereas it significantly decreased the incidence of wound infections (two out of 45 *versus* nine out of 47). In 1991, AZNAR [32] performed a prospective, randomised, double-blind trial of cefazolin 1 g *i.v.* 30 min prior to surgery *versus* placebo [32]. A statistically significant decrease in empyema (14% *versus* 7%) and pneumonia (9% *versus* 4%) was observed in the active treatment arm. The occurrence of wound infection was also lowered by prophylaxis: one (1.5%) out of 70 in the antibiotic prophylaxis arm *versus* eight (14%) out of 57 in the placebo group.

Thus, despite the small number of randomised clinical trials and initial conflicting data, the majority of studies support the use of peri-operative antibiotics in general thoracic surgery. The evidence is strong for prevention of wound infection, but much more limited for empyema and POP. It must be outlined that these different types of infectious complications contribute very differently to life-threatening situations and mortality. In addition, this contribution also depends on the extent of resection, making interpretation of available data more difficult. Some comments on the influence of the extent of resection can be proposed, but they are merely derived from commonly accepted thoracic surgical experience and not by specific studies.

Influence of the extent of lung resection on the potential usefulness of antibiotic prophylaxis

The influence of the extent of lung resection (lobectomy *versus* pneumonectomy) can be discussed in view of the types and mechanisms of post-operative thoracic infections.

Simple wound infection

"Simple" wound infection is a relatively benign condition, especially in nonpneumonectomy patients: the diagnosis is easy and simple local treatment (drainage and dressing) often deals successfully with the condition. In pneumonectomy patients, even a superficial wound infection carries a significant risk of major complication, as deep diffusion of the infection in the empty pleural cavity is frequent and leads to empyema (without BPF), a life-threatening condition in these patients: thus, the importance of preventing wound infections and their possible consequences is substantially different with respect to the extent of resection.

Empyema

In the absence of wound infection, empyema has different mechanisms and pathophysiology in lobectomy and pneumonectomy patients, with possibly different impact of antibiotic prophylaxis. Empyema is usually associated with the occurrence of BPF in lobectomy patients (empyema with fistula), but empyema without BPF does exist, almost exclusively after pneumonectomy.

Empyema without fistula

Following lobectomy, if expansion of the remaining lung parenchyma achieves occupation of the whole pleural cavity with no residual space, the occurrence of empyema without fistula is a rare event. In this context, the impact of antibiotic prophylaxis is probably minimal, provided that meticulous surgical technique, accompanied by lung decortication if needed to obtain optimal parenchymal expansion, almost completely prevents air leaks at the end of the procedure.

The situation is radically different in pneumonectomy patients, where the pleural space is empty: in this case, intra-operative contamination may easily lead to empyema without fistula, supporting the paramount importance of antibiotic prophylaxis. Finally, in the early post-operative period, bacteraemia secondary to procedures (*e.g.* bladder or gastric catheterisation) or post-operative nonthoracic infections (*e.g.* urinary tract infections) may lead to infection of the empty cavity. Facing these situations, the impact of intra-operative antibiotic prophylaxis is probably limited.

Empyema with fistula

Empyema with fistula generally occurs in the late post-operative period (*i.e.* after the fifth–seventh post-operative day). Indeed, early BPF is highly infrequent and generally secondary to a technical error in bronchial stump handling and suture. In both instances, antibiotic prophylaxis probably has limited direct impact on the occurrence of this complication. However, antibiotic prophylaxis might prove indirectly useful through reducing the risk of POP, and especially POP requiring mechanical ventilation, as mechanical ventilation is known to increase the risk of BPF.

Choice of drugs: focus on comparative studies

In patients with no known pulmonary or pleural infection at the time of operation, lung resection is a clean–contaminated surgery, with contamination of surgical site (wound, chest wall and/or pleura) possibly occurring by seeding of bacteria from the skin or bronchial tree. In particular, when a bronchus is sectioned and sutured, the degree and length of contamination depend on the surgical technique and especially whether staplers, and also their type, or stitches are used. Thus, when choosing a drug for antibiotic prophylaxis, pathogens colonising both the skin (*S. aureus* and *Staphyloccus epidermidis*) and the bronchial tree should be taken into account. Pathogens possibly colonising the airways depend on the ecology of specific populations, but *S. pneumoniae* and *H. influenzae* are frequent in most populations undergoing lung resection, keeping in mind the significant percentage of COPD patients among surgical candidates [33]. Only a few studies compared different antibiotics in the context of lung resection.

Cephalosporins are generally thought to provide adequate coverage of these micro-organisms and, therefore, are often proposed for antibiotic prophylaxis in lung resection. Cephalosporins differ in their spectrum of antibacterial activity, with first–second generations being more active against Gram-positive bacteria and third–fourth generations being more active against Gram-negative

bacteria. Historically, the first–second generation cefalosporins have been more frequently used. Based on the above-mentioned differences in spectrum of antibacterial action, a randomised trial was carried out to compare the second-generation cephalosporin cefuroxime to the fourth-generation cefepime (both administered over a 48-h period). Altogether, 102 patients were randomised, 50 in the cefuroxime group and 52 in the cefepime group. Two (3.8%) empyemas occurred in the cefepime group while no case was observed in the cefuroxime group ($p=0.16$). Overall infection rates (pneumonia+bronchopneumonia+empyema) were 14.0% and 26.7% in the cefuroxime and the cefepime groups, respectively ($p=0.12$). 12 pathogenic bacterial strains were isolated in the cefepime group, whereas only five were isolated in the cefuroxime group ($p=0.04$). These results prompted the authors to state that cefuroxime was marginally more effective than cefepime, but presented an additional cost advantage [34].

In a detailed analysis of the literature, we found a highly variable incidence of pneumonia after lung surgery, depending not only on the extent of resection and the type of antibiotic prophylaxis, but also on the modalities of microbiological sampling and on type of study design (prospective or retrospective) [5]. In a subsequent prospective observational study of 168 patients undergoing major lung resection, we used antibiotic prophylaxis with a second-generation cephalosporin cefamandol, 1.5 g at induction of anaesthesia and 3 g per 24 h for 48 h post-operatively [35]. The overall incidence of POP was <5% (42 out of 168). Microbiologically documented and nondocumented pneumonias were recorded in 24 and 18 cases, respectively. *Haemophilus* species, *Streptococcus* species and, to a much lesser extent, *Pseudomonas* and *Serratia* species were the most frequently identified pathogens. Interestingly, bronchial colonisation was identified on pre-operative bronchial samples in 31 of 136 patients (22.8%) and POP occurred in 15 out of 31 and 20 out of 105 cases among colonised and noncolonised patients, respectively ($p=0.001$). Multivariate analysis found that risk factors for POP were the extent of resection, male sex, presence of COPD and presence of colonising bacteria on the intra-operative sampling. Furthermore, in colonised patients, early POP was often related to colonising bacteria. Reduced sensitivity or resistance of these pathogens to cefamandol was frequent. Based on these data, we decided to change our antibioprophylaxis, using a short (24-h) high-dose (6-g) course of amoxicilline–clavulanate, which targets the bacteria that were most often responsible for pre-operative colonisation in our own patient population. A significant decrease in the incidence of both microbiologically documented and nondocumented POP was observed, as well as a significant decrease in the overall need of post-operative antibiotics. Conversely, the proportion of bacterial documentation among cases of POP and the occurrence of bronchitis, wound infections, empyema and the need for antibiotics for nonrespiratory causes did not change [35].

Individualised strategies

The above-mentioned study [35] outlined that COPD and bronchial colonisation were risk factors for developing POP. Similar results were found by a team of the Chiba University in Japan, who retrospectively evaluated 626 patients with lung cancer treated by surgery [7]. They found that POP occurred in 6.4% of patients, with significant differences between COPD (14.3%) and non-COPD patients (3.6%). Although the technique of sampling of bronchial secretions was not standardised, they found that 12.8% of patients were colonised pre-operatively by PPMs. As expected, this rate was significantly higher in COPD patients (19.9%) when compared with non-COPD patients (10.9%). These authors also found that *S. pneumoniae* and *H. influenzae* were the micro-organisms more frequently responsible for the initial colonisation. Interestingly, they also observed that POP occurred more frequently among colonised patients (11.5% *versus* 5.7%). These data suggest that optimisation of COPD treatment and targeting bacteria responsible for bronchial colonisation in these patients when choosing antibiotic prophylaxis should be regarded as important strategies to lower the incidence of POP. Currently, a French multicentre, randomised, double-blind, placebo-controlled study is ongoing to assess the efficacy of pre-operative and early post-operative chlorhexidine mouthwash and nasal toilette.

Duration and timing of peri-operative antibiotics

Several studies provided evidence on the efficacy of single-dose prophylactic antibiotics in nonthoracic operations. Two randomised studies addressed this issue in thoracic surgery: one compared cefazolin 1 g *i.v.* prior to induction to cefazolin 1 g *i.v.* at induction and every 8 h for a total of six doses; the other compared ampicillin/sulbactam 3 g at induction only with ampicillin/sulbactam 3 g at induction and every 8 h for a total of three doses. Both showed no differences in terms of wound infection, pneumonia or empyema between the two arms [36, 37]. However, some specific features of lung resection have to be considered: first, both operation and anaesthesia (positioning of double lumen tube, fibreoptic checking of its position, epidural analgesia, central venous catheter insertion and monitoring) are often long-lasting; and, secondly, prolonged single-lung ventilation probably favours bacterial growth in the deflated lung. Thus, it might be important to maintain concentrations greater than the minimum inhibitory concentration during at least 24 h, either through multiple doses and/or through a high initial dose. This explains why, in our above-described study, we used high dose (6 g per 24 h) amoxicillin–clavulanate. This choice was also supported by the necessity of taking into account the high frequency of *S. pneumoniae* with reduced sensitivity to penicillin, a characteristic observed not only in our study but also in other national surveys [38].

Another issue is the precise timing of peri-operative antibioprophylaxis, *i.e.* a while (*e.g.* 30 min) before induction, as in the paper by AZNAR *et al.* [32], or immediately before or at induction, as in other above-mentioned studies [34, 35]. This interesting debate can take advantage of pharmacokinetic data on the timing of antibiotic peaks relative to that of endotoxinemia during surgery, but comparative clinical studies will be required.

Conclusions

Post-operative thoracic infections including pneumonia and empyema are frequent and represent an important source of mortality. Although the number of randomised controlled trials in this area is relatively limited, currently available evidence supports the role of prophylactic antibiotics (mostly first- or second-generation cephalosporins) in patients undergoing lung resection surgery.

Additional studies would be useful to determine the optimal strategies in terms of antibiotic choice, timing and duration of prophylactic treatment, depending on individual risk factors, local microbial ecology and type of surgery.

Statement of Interest
None declared.

References

1. Arozullah AM, Khuri SF, Henderson WG, *et al.* Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. *Ann Intern Med* 2001; 135: 847–857.
2. Lee JY, Jin SM, Lee CH, *et al.* Risk factors of postoperative pneumonia after lung cancer surgery. *J Korean Med Sci* 2011; 26: 979–984.
3. Díaz-Ravetllat V, Ferrer M, Gimferrer-Garolera JM, *et al.* Risk factors of postoperative nosocomial pneumonia after resection of bronchogenic carcinoma. *Respir Med* 2012; 106: 1463–1471.
4. Stephan F, Boucheseiche S, Hollande J, *et al.* Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. *Chest* 2000; 118: 1263–1270.
5. Schussler O, Alifano M, Dermine H, *et al.* Postoperative pneumonia after major lung resection. *Am J Respir Crit Care Med* 2006; 173: 1161–1169.
6. Radu DM, Jaure guy F, Seguin A, *et al.* Postoperative pneumonia after major pulmonary resections: an un-solved problem in thoracic surgery. *Ann Thorac Surg* 2007; 84: 1669–1673.
7. Yamada Y, Sekine Y, Suzuki H, *et al.* Trends of bacterial colonisation and the risk of postoperative pneumonia in lung cancer patients with chronic obstructive pulmonary disease. *Eur J Cardiothorac Surg* 2010; 37: 752–757.

8. Deschamps C, Allen MS, Trastek VF, *et al.* Empyema following pulmonary resection. *Chest Surg Clin North Am* 1994; 4: 583–592.
9. Cerfolio RJ. The incidence, etiology and prevention of postresectional bronchopleural fistula. *Semin Thorac Cardiovasc Surg* 2001; 13: 3–7.
10. Kutlu CA, Williams EA, Evans TW, *et al.* Acute lung injury and acute respiratory distress syndrome after pulmonary resection. *Ann Thorac Surg* 2000; 69: 376–380.
11. Wang J, Olak J, Ultmann RE, *et al.* Assessment of pulmonary complications after lung resection. *Ann Thorac Surg* 1999; 67: 1444–1447.
12. Dupont H, Montravers P, Gauzit R, *et al.* Club d'Infectiologie en Anesthésie-Réanimation. Outcome of postoperative pneumonia in the Eole study. *Intensive Care Med* 2003; 29: 179–188.
13. Belda J, Cavalcanti M, Ferrer M, *et al.* Bronchial colonization and postoperative respiratory infections in patients undergoing lung cancer surgery. *Chest* 2005; 128: 1571–1579.
14. Auriant I, Jallot A, Herve P, *et al.* Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med* 2001; 164: 1231–1235.
15. Lefebvre A, Lorut C, Alifano M, *et al.* Noninvasive ventilation for acute respiratory failure after lung resection: an observational study. *Intensive Care Med* 2009; 35: 663–670.
16. Regnard JF, Alifano M, Puyo P, *et al.* Open window thoracostomy followed by intrathoracic flap transposition in the treatment of empyema complicating pulmonary resection. *J Thorac Cardiovasc Surg* 2000; 120: 270–275.
17. Pierson DJ, Horton CA, Bates PW. Persistent bronchopleural air leak during mechanical ventilation. A review of 39 cases. *Chest* 1986; 90: 321–323.
18. Gossot D, Stern JB, Galetta D, *et al.* Thoracoscopic management of postpneumonectomy empyema. *Ann Thorac Surg* 2004; 78: 273–276.
19. D'Journo XB, Rolain JM, Doddoli C, *et al.* Airways colonizations in patients undergoing lung cancer surgery. *Eur J Cardiothorac Surg* 2011; 40: 309–319.
20. Wansbrough-Jones MH, Nelson A, New L, *et al.* Bronchoalveolar lavage in the prediction of post-thoracotomy chest infection. *Eur J Cardiothorac Surg* 1991; 5: 433–434.
21. Sok M, Dragas AZ, Erzen J, *et al.* Sources of pathogens causing pleuropulmonary infections after lung cancer resection. *Eur J Cardiothorac Surg* 2002; 22: 23–27.
22. Ioanas M, Angrill J, Baldo X, *et al.* Bronchial bacterial colonization in patients with resectable lung carcinoma. *Eur Respir J* 2002; 19: 326–332.
23. Dancewicz M, Szymankiewicz M, Bella M, *et al.* Bronchial bacterial colonization in patients with lung cancer. *Pneumonol Alergol Pol* 2009; 77: 242–247.
24. Sato M, Saito Y, Fujimura S, *et al.* Study of postoperative bronchopleural fistulas-analysis of factors related to bronchopleural fistulas. *Nippon Kyobu Geka Gakkai Zasshi* 1989; 37: 498–503.
25. Baumann MH, Sahn SA. Medical management and therapy of bronchopleural fistulas in mechanically ventilated patient. *Chest* 1990; 97: 721–728.
26. Bernard AC, Deschamps C, Allen MS, *et al.* Pneumonectomy for malignant disease: factors affecting early morbidity and mortality. *J Thorac Cardiovasc Surg* 2001; 121: 1076–1082.
27. Kvale P, Ranga V, Kopacz M, *et al.* Pulmonary resection. *South Med J* 1977; 70: 64–69.
28. Truesdale R, D'Alessandri R, Manuel V, *et al.* Antimicrobial *vs* placebo prophylaxis in noncardiac thoracic surgery. *JAMA* 1979; 241: 1254–1256.
29. Cameron J, Imbembo A, Keiffer R, *et al. Prospective clinical trial of antibiotics for pulmonary resection. Surg Gynecol Obstet.* 1981; 152: 156–158.
30. Ilves R, Cooper JD, Todd TR, *et al.* Prospective, randomized, double-blind study using prophylactic cephalothin for major, elective, general thoracic operations. *J Thorac Cardiovasc Surg* 1981; 81: 813–817.
31. Frimodt-Møller N, Ostri P, Pedersen I, *et al.* Antibiotic prophylaxis in pulmonary surgery: a double-blind study of penicillin *versus* placebo. *Ann Surg* 1982; 195: 444–450.
32. Aznar R, Mateu M, Miro J, *et al.* Antibiotic prophylaxis in non-cardiac thoracic surgery: cefazolin *versus* placebo. *Eur J Cardiothorac Surg* 1991; 5: 515–518.
33. Engelman R, Shahian D, Shemin R, *et al.* The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part ii: antibiotic choice. *Ann Thorac Surg* 2007; 83: 1569–1576.
34. Turna A, Kutlu C, Ozalp T, *et al.* Antibiotic prophylaxis in elective thoracic surgery: cefuroxime *versus* cefepime. *Thorac Cardiovasc Surg* 2003; 51: 84–88.
35. Schussler O, Dermine H, Alifano M, *et al.* Should we change antibiotic prophylaxis for lung surgery? Postoperative pneumonia is the critical issue. *Ann Thorac Surg* 2008; 86: 1727–1733.
36. Olak J, Jeyasingham K, Forrester-Wood C, *et al.* Randomized trial of one-dose *versus* six-dose cefazolin prophylaxis in elective general thoracic surgery. *Ann Thorac Surg* 1991; 51: 956–958.
37. Wertzel H, Swoboda L, Joos-Wurtemberger A, *et al.* Perioperative antibiotic prophylaxis in general thoracic surgery. *Thorac Cardiovasc Surg* 1992; 40: 326–329.
38. Laurens G, Murbach V, Cattier B, *et al.* Observatoires régionaux du Pneumocoques: surveillance de la sensibilité aux antibiotiques des pneumocoques isolés en situation pathogène en France en 1999. [Regional Observatories Pneumococcus: a survey of antibiotic sensitivity of *Streptococcus pneumoniae* isolated in pathogenic situations in France, 1999.] *BEH* 2001; 33: 155–159.

Chapter 2

Medical treatment of pulmonary tuberculosis

*Giovanni Sotgiu**, Rosella Centis*#, *Lia D'Ambrosio*# and *Giovanni Battista Migliori*#

SUMMARY: Tuberculosis (TB) remains among the leading causes of death among treatable infectious diseases. Treatment of pulmonary TB has progressed enormously from the initial monotherapy options offered in the 1940s. However, while a standard 6-month course of chemotherapy has proved to be extremely effective in treating drug-susceptible TB cases, the appearance of drug-resistant TB has complicated the management of pulmonary TB. Rapid drug susceptibility testing is strongly advised in order to avoid inadequate treatment at the time of TB diagnosis, and the regimen prescribed should include at least four potentially active drugs and have an increased duration of treatment. Drug–drug interactions between anti-TB and anti-HIV drugs also increase poor treatment outcome rates and the occurrence of adverse events. However, therapeutic drug monitoring can be used as a diagnostic tool to assess the dosing, through evaluation of blood concentrations. Despite the growing problem of drug resistance, hope is generated by the growing evidence that old drugs may still be useful and that new effective and well-tolerated drugs are now available. Today, patients can benefit from novel drugs and regimens, but it is necessary to administer them carefully to avoid the real risk of losing their effectiveness in a time shorter than that necessary to develop them.

*Clinical Epidemiology and Medical Statistics Unit, Dept of Biomedical Sciences, University of Sassari, Research, Medical Education and Professional Development Unit, L'Azienda Ospedaliero Universitaria di Sassari, Sassari, and #World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy.

Correspondence: G.B. Migliori, World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Via Roncaccio 16, 21049 Tradate, Italy. Email: giovannibattista.migliori@fsm.it

Eur Respir Monogr 2013; 61: 11–19.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040212
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The aetiological agent of pulmonary tuberculosis (TB) was identified as *Mycobacterium tuberculosis* about 130 years ago by Robert Koch in Berlin, and effective anti-TB drugs have been discovered and globally distributed since the 1940s. However, TB remains one of the leading causes of morbidity and mortality, alongside HIV/AIDS and malaria, with over 8.7 million new TB cases and 1.4 million deaths in 2011 [1–6].

The aim of this chapter is to describe the principles and rationale for TB chemotherapy, and the suggested regimens to treat drug-susceptible and -resistant cases of pulmonary TB. In addition, the new anti-TB drugs and the perspectives for new, shorter regimens will be also described.

Definitions

Pulmonary TB is a lung disease caused by *M. tuberculosis* strains. Clinical and radiological signs can be helpful if TB is suspected; however, only bacteriology can confirm the diagnosis [7–9].

Infectious TB refers to the fact that *M. tuberculosis* strains are transmitted from patients with pulmonary TB in the majority of cases. The most infectious cases are those with cavitary lesions in the lung parenchyma, excreting a high load of mycobacteria (with positivity of the sputum smear and culture examinations). Patients who are sputum smear negative but culture positive are deemed less infectious [7–9].

Treatment outcomes for pulmonary TB represent standardised, mutually exclusive clinical results following a course of anti-TB therapy. Positive outcomes are: 1) cured, when a sputum smear and culture results are negative at the end of therapy; 2) treatment completed, in cases where >80% of the prescribed doses are taken under direct observation, although the evidence of a bacteriological conversion is missing. The sum of the cured and treatment completed case rates represents the treatment success rate. Negative outcomes are: 1) died, when a patient under TB therapy dies for any cause; 2) defaulted, when a patient interrupts anti-TB therapy for at least 2 months without medical approval; and 3) failed, when a patient is bacteriologically positive after months of anti-TB therapy [10]. Relapse refers to a case previously diagnosed as treatment success who is then diagnosed with TB at any time after the first episode.

Pan-susceptible TB is TB caused by *M. tuberculosis* strains susceptible to all first-line anti-TB drugs [11]. Multidrug-resistant (MDR)-TB is TB caused by *M. tuberculosis* strains resistant to at least the two first-line anti-TB drugs isoniazid and rifampicin [9, 12, 13]. Extensively drug-resistant (XDR)-TB is TB caused by *M. tuberculosis* resistant to isoniazid and rifampicin, plus any fluoroquinolone, and at least one of the three injectable second-line drugs (amikacin, capreomycin and kanamycin) [13–15].

TB elimination is the point at which fewer than one sputum smear-positive case per million inhabitants emerges annually in the general population, or when the prevalence of TB in the general population is below 1% and continues to decrease [7, 8].

The rationale behind the polytherapeutic approach against pulmonary TB

M. tuberculosis is a slow-growing micro-organism, whose replication is favoured by an aerobic environment. The mycobacterial population identified in the lung parenchyma is heterogeneous, being characterised by bacteria with a different metabolism [16]. Active and dormant bacteria have been described, which can only be killed through a prolonged, multidrug therapy [16]. In the 1960s, several clinical trials, particularly the Edinburgh Method of John Crofton, demonstrated that the combination of at least two anti-TB drugs is needed to prevent the emergence of drug-resistant strains and, consequently, clinical failure [8, 17].

Adherence to the current therapeutic prescriptions (*i.e.* daily dosages, drug combination and treatment duration) could increase the chances of bacterial eradication, avoiding bacterial and clinical relapses that are frequently associated with the emergence of drug-resistant strains owing to sub-therapeutic drug concentrations. However, apart from the role of pharmacokinetic and pharmacodynamic factors, other relevant variables can influence the treatment outcome of pulmonary TB cases, including those related to mycobacterial load and metabolism [7, 8, 18].

Anti-TB drugs should show one or more of the following pharmacodynamic characteristics [7, 8, 18]: 1) rapidly kill growing mycobacteria, as performed, for instance, by isoniazid, pyrazinamide, rifampicin and streptomycin (bactericidal drugs); 2) rapidly kill semi-dormant organisms, as performed by pyrazinamide and rifampicin (sterilising drugs); and 3) prevent the emergence of drug-resistant strains, as performed by ethambutol, isoniazid, para-aminosalicylic acid, pyrazinamide, rifampicin, streptomycin and thiacetazone.

Pulmonary TB must be treated with different drugs in different situations, and the length of exposure can vary. Generally, two therapeutic phases are recognised for drug-sensitive TB. The first is the intensive phase, whose final goal is the bacteriological elimination of growing and

semi-dormant mycobacteria. It is crucial from a clinical and public health perspective, favouring the clinical recovery, reducing the infectiousness of the patient, and preventing the emergence and spread of drug-resistant strains, whose probability of occurrence depends on bacterial load. Ethambutol, isoniazid, pyrazinamide and rifampicin are usually prescribed in this phase. The second phase is the continuation phase, whose final goal is the bacteriological elimination of residual mycobacteria. The emergence of drug resistance is rare, as a consequence of the low mycobacterial burden, and two potent anti-TB drugs can be prescribed in patients not previously exposed to anti-TB therapy [10]. In case of monoresistance to a drug, usually prescribed during the intensive phase, the probability of a positive outcome is high if four drugs are prescribed in the intensive phase [9]. The World Health Organization (WHO) classifies anti-TB drugs into five groups, whose characteristics are shown in table 1.

Table 1. Classification and safety profile of antituberculosis drugs

	Chemical classification	Mean daily dosage	Adverse events
Group 1			
Isoniazid	Hydrazide of isonicotinic acid	5 mg·kg^{-1}	Peripheral neuropathy, liver dysfunction, skin rash, sleepiness
Rifampicin	Rifamycin	10 mg·kg^{-1}	Liver dysfunction, flu syndrome, skin rash, thrombocytopenic purpura, orange staining of urine
Ethambutol	Ethanediamine	15–25 mg·kg^{-1}	Retro-bulbar neuritis
Pyrazinamide	Pyrazine	30–40 mg·kg^{-1}	Liver dysfunction, arthralgia
Group 2			
Streptomycin	Aminoglycoside	15–20 mg·kg^{-1}	Renal dysfunction, skin rash, vestibular and auditory dysfunction
Amikacin	Aminoglycoside	15–20 mg·kg^{-1}	Renal dysfunction, skin rash, vestibular and auditory dysfunction
Kanamycin	Aminoglycoside	15–20 mg·kg^{-1}	Renal dysfunction, skin rash, vestibular and auditory dysfunction
Capreomycin	Cyclic peptide	15–20 mg·kg^{-1}	Renal dysfunction, vestibular and auditory dysfunction
Group 3			
Ofloxacin Ciprofloxacin Gatifloxacin Moxifloxacin	Fluroquinolone	400–1000 mg	Nausea, vomiting, skin rash, psychosis
Group 4			
Ethionamide	Thiocarbamide	15–20 mg·kg^{-1}	Gastritis
Prothionamide	Thiocarbamide	15–20 mg·kg^{-1}	Gastritis
Cycloserine	Alanine analogue	500–1000 mg	Psychosis
Para-aminosalicylic acid	Aminosalicylic acid	150 mg·kg^{-1}	Liver dysfunction, gastrointestinal disorders, thyroid goitre, haematological disorders
Group 5			
Linezolid	Oxazolidone	600 mg	Peripheral neuropathy, gastrointestinal disorders, haematological disorders
Clofazimine	Phenazine	200–300 mg	Eosinophilic enteritis, gastrointestinal disorders, discoloration of the skin
Amoxicillin/clavulanate	β-lactam	875/125 mg twice daily or 500/125 mg three times daily	Gastrointestinal disorders, skin rash
Clarithromycin	Macrolide	500 mg twice daily	Gastrointestinal disorders, facial swelling
Terizidone	Isoxazole	600–900 mg	Gastrointestinal disorders, psychosis
Thiacetazone	Thiosemicarbazone	150 mg	Gastrointestinal disorders, skin rash, arthro-myalgia, tingling
Thioridazine	Piperidine	75 mg	Akathisia, impotence, QT interval prolongation, autonomic side-effects

Drug–drug interactions between anti-TB and anti-HIV drugs

One of the most important causes of death in HIV-positive patients is TB disease. The last WHO global report on TB highlighted that the estimated incidence of TB in individuals infected with HIV was 1.1 million cases in 2011; the number of deaths was estimated to be 430 000 [1]. The natural history of HIV infection has been modified since 1996, with the introduction in the market of protease inhibitors and the prescription of an individualised combination of antiretrovirals (the so-called highly active antiretroviral therapy (HAART)) [19, 20]. The clinical efficacy of the antiretroviral drugs has significantly contributed to reduction in the incidence of opportunistic diseases, including TB [21]. However, the unavailability of the antiretroviral drugs in low-income countries is the main basis of the poor epidemiological indicators. In contrast, low adherence to the anti-HIV drugs, particularly in those patients with several comorbidities, who are exposed to a relevant pill burden with drug-related toxicities, can justify poor clinical outcomes in high-income countries.

Pharmacological interactions between anti-TB and anti-HIV drugs have been extensively described and are explained as the consequence of different singular or concomitant pathogenetic events [22]. In particular, it was shown that the first potential pharmacokinetic problem can occur in the gastrointestinal tract, where an abnormal pH in the stomach or in the intestine, as well as malabsorption due to diarrhoea, can hinder the optimal blood concentrations of the drugs. Another relevant interaction is related to interference with the hepatic cytochrome CYP450, which is linked to induction or inhibition of drug metabolism. Rifampicin and protease inhibitors are well-known as inducer and inhibitor, respectively, and are able to reduce and to increase blood concentrations of the drugs. The former can increase poor treatment outcome rates, whereas the latter can augment the chance of occurrence of adverse events.

Several reports have pointed out the interactions between rifampicin and protease inhibitors [23–25], non-nucleoside reverse transcriptase inhibitors [26], integrase inhibitors [27] and CCR-5 receptor antagonists [22, 28]. Despite these interactions and their potential clinical consequences, it has been proved that rifampicin-sparing regimens are ineffective [22, 29–31]. The reduction of peak and trough concentrations for efavirenz and nevirapine, and, consequently, the reduced pharmacodynamic effect, can be bypassed by increasing the concentration of anti-HIV drugs, even if a high risk of adverse events is expected [22, 26]. The negative effect of rifampicin on HIV protease inhibitors could be reduced by the concomitant administration of a high dose of ritonavir; its protective effect was demonstrated as a consequence of the increased half-life of the co-administered protease inhibitors. From a pathogenetic perspective, ritonavir can reduce the activity of the hepatic cytochrome CP3A4. Therapeutic drug monitoring can be used as a potent diagnostic tool to assess the dosing of the drugs, through evaluation of the blood concentrations [32]. This individualised approach can be associated with a decreased risk of adverse events, linked to an altered pharmacokinetic profile.

Another significant interaction has been described between rifampicin and zidovudine. The increased rifampicin-related glucuronidation reduces the blood concentration of zidovudine [22, 33].

The most frequent and serious adverse events observed in co-infected patients were liver dysfunction (mainly in those treated with non-nucleoside reverse transcriptase inhibitors, isoniazid, pyrazinamide, ethambutol and rifampicin), peripheral neuropathy (mainly associated with stavudine, didanosine and isoniazid), gastrointestinal, central nervous system and haematological disorders, and hypersensitivity events [22].

Treatment of drug-resistant TB with the current drugs is associated with poor clinical outcomes. Furthermore, drug–drug interactions can be associated with an increased rate of adverse events (for example, the concomitant administration of nephrotoxic drugs, such as tenofovir and second-line injectable aminoglycosides, can favour the occurrence of renal dysfunction) [22, 34]. A baseline assessment (*i.e.* hepato-renal profile and hepatitis B and C virus serology) and strict clinical monitoring is necessary, since the scientific evidence on this topic is poor and not systematic.

Treatment guidelines

A summary of the recommended treatment regimens for new and previously treated TB patients is shown in table 2. Treatment will be selected depending on whether the TB is likely to be drug-susceptible TB [35] or MDR-TB [36].

Drug-susceptible TB

Patients diagnosed with pulmonary TB, not previously exposed to anti-TB drugs for more than 1 month (new cases), should be treated with a 6-month rifampicin-containing regimen. In particular, it should include the association of isoniazid, rifampicin, pyrazinamide and ethambutol for the first 2 months (the intensive phase), followed by the association of isoniazid and rifampicin for the remaining 4 months (the continuation phase). Longer durations (*i.e.* more than 6 months) are not recommended because they do not demonstrate clinical superiority. The international recommendations suggest a daily dosage for the entire duration of therapy, particularly during the intensive phase; however, a three times weekly phase could be performed provided that a direct observation could be implemented. These recommendations are valid for TB/HIV co-infected patients, including the duration of therapy and the daily dosage for the intensive and continuation phases.

Patients who had positive sputum smear examination results should be evaluated at the end of the intensive phase in order to assess smear and culture conversion. Positivity of the smear examination after 2 months should not represent a criterion for the extension of TB therapy duration. Patients treated for more than 1 month with anti-TB therapy should be carefully evaluated: a collection of biological samples for culture and drug susceptibility testing (rapid and/or conventional) is strongly recommended before prescribing a new regimen.

In case of relapse or default, patients could be initially treated with an empirical regimen (*i.e.* isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin for 2 months, followed by isoniazid, rifampicin, pyrazinamide and ethambutol for 1 month, then isoniazid, rifampicin and ethambutol for 5 months), provided that the local proportion of multidrug resistance is low.

MDR- and XDR-TB

MDR-TB is a relevant clinical and public health issue, with 630 000 people estimated by WHO to suffer from this severe form, *i.e.* about 3.7% of new cases and 20% of re-treated cases. Out of the

Table 2. Recommended treatment regimens for new and previously treated tuberculosis (TB) patients

	Drugs	Duration months
New cases		
Intensive phase	Ethambutol[#], isoniazid, pyrazinamide and rifampicin	2[¶]
Continuation phase	Isoniazid and rifampicin, with or without ethambutol	4
Previously treated cases		
High probability of MDR-TB (failure)	Pending drug susceptibility test results: empirical MDR-TB regimen[+]	
Medium or low probability of MDR-TB (relapse or default)	Ethambutol, isoniazid, pyrazinamide, rifampicin and streptomycin[+]	2
	Ethambutol, isoniazid, pyrazinamide and rifampicin[+]	1
	Ethambutol, isoniazid and rifampicin[+]	5

Table adapted from [35]. MDR: multidrug-resistant. [#]: ethambutol has to be prescribed in individuals with non-cavitary, smear-negative pulmonary TB or with extra-pulmonary TB; in TB meningitis, it should be replaced by streptomycin. [¶]: level of isoniazid resistance among new TB cases is elevated and *in vitro* isoniazid susceptibility testing is not available. [+]: to be changed once drug susceptibility test results are available.

MDR-TB cases, 9% harbour XDR-TB strains. About 60% of the MDR-TB cases occurred in Brazil, China, India, the Russian Federation and South Africa alone (the "BRICS" countries).

MDR-TB should be adequately treated to avoid the emergence of further resistance and the spread of drug-resistant strains to close contacts. However, anti-TB drugs for MDR-TB patients, usually prescribed on the basis of the drug susceptibility testing, are more toxic, more expensive and, being less effective, need to be administered for prolonged periods. Unfortunately, as of today, the success rate for MDR-TB cases is lower than 50% and that of XDR-TB cases is even lower [37–39]. Adverse events may lower the adherence of the patients to their treatment, increasing the probability of treatment failure and favouring the possibility of emergence of further resistance.

Rapid drug susceptibility testing of isoniazid and rifampicin, or of rifampicin only, is strongly advised in order to avoid inadequate treatment at the time of TB diagnosis. To assess the efficacy of the prescribed regimen, culture-based bacteriological monitoring is advised, rather than sputum smear microscopy. The regimen prescribed should include at least four potentially active drugs. In particular, it is suggested that during the intensive phase the following should be administered: pyrazinamide and an injectable second-line drug (*i.e.* amikacin, capreomycin or kanamycin), a later-generation fluoroquinolone as well as ethionamide (or prothionamide), and cycloserine (or para-aminosalicylic acid). The drugs categorised as group five should be included only if four potential active drugs are missing among those suggested. The duration of the intensive phase should be at least 8 months, and can be increased depending on culture conversion. An analogous criterion is recommended for the duration of the entire treatment (intensive and continuation phases), which should be at least 20 months, extendable depending on the bacteriological status. Patients previously exposed to an MDR-TB therapy should be treated for more months than those naive to MDR-TB regimens. Antiretroviral therapy for TB/HIV co-infected patients should be started within 8 weeks of the administration of the first anti-TB drugs; no CD4 cell count-specific restrictions exist.

New drugs and potential new regimens to treat pulmonary TB

The need for new drugs and potential new regimens is intuitive if it is considered that the new world record of MDR-TB prevalence, described in Belarus, is 35.3% among new cases and 76.5% among previously treated cases [40]. In addition, another relevant emerging issue is represented by the so-called totally drug-resistant (TDR)-TB cases, *i.e.* patients infected by mycobacterial strains resistant to all anti-TB drugs. This alarming epidemiological phenomenon has already been described in Italy, Iran and India [41]. However, the acronym TDR-TB, not recommended by the WHO, was replaced by the term "resistance beyond XDR-TB" [38], as the bacteriological criteria necessary to define resistance to all anti-TB drugs are difficult to standardise; furthermore, the labelling of these cases as incurable can increase stigma. Given the need to prescribe a sufficient number of active drugs into an effective regimen, the availability of new drugs is crucial.

After over 40 years of neglect, the commitment of the WHO and other stakeholders, including pharmaceutical companies, will allow the introduction of new drugs into the market in the near future. The first group of new drugs is currently used off-label to treat pulmonary TB, including linezolid, meropenem and cotrimoxazole. Linezolid is effective, but unfortunately hampered by severe adverse events, as a recent meta-analysis of all the individual data of the cases so far published and an experimental study have demonstrated [42, 43]. Conversely, meropenem has shown promising efficacy, safety and tolerability in a recently published case–control study when added to linezolid-containing regimens [44]. Cotrimoxazole, an old molecule used for other bacterial and protozoal infections, has also demonstrated some potential in treating MDR-TB cases [45].

A group of really new drugs, which are in the last phases of development, is represented by bedaquiline, delamanid and PA-824. The first evidence on the effectiveness of delamanid was provided by GLER *et al.* [46], who demonstrated that this new drug, in combination with a background regimen developed according to the WHO guidelines [36], is associated with an increased sputum culture conversion at 2 months in patients with MDR-TB. Another study by SKRIPCONOKA *et al.* [47] showed its efficacy in MDR-TB cases and its ability to reduce mortality in these difficult-to-treat cases.

Bedaquiline, also known as TMC-207, has been recently approved by the US Food and Drug Administration. Its efficacy was shown in two recent studies published in 2009 and 2012 [48, 49]. The former demonstrated that it could increase the proportion of culture conversion in MDR-TB cases (48% *versus* 9% in the placebo-based arm; hazard ratio 11.8) [48]. The latter described the efficacy and safety results after a 2-year follow-up of 47 MDR-TB patients: the positive treatment outcomes were confirmed as well as the low proportion of adverse events, with only the exception of nausea [49]. A striking finding was the prevention of the emergence of drug resistance for the companion drugs [49].

In terms of new regimens, a recent study by DIACON *et al.* [50] evaluated the 14-day early bactericidal activity of PA-824 plus moxifloxacin and pyrazinamide, which proved to be significantly higher than that of bedaquiline, bedaquiline and pyrazinamide, PA-824 and pyrazinamide, and bedaquiline and PA-824, and comparable to that of the standard treatment regimen of isoniazid, rifampicin and pyrazinamde with streptomycin or ethambutol. An additional, important finding of the study is that the addition of pyrazinamide increased the activity of both bedaquiline and PA-824. This innovative approach, which allows the testing of several drugs at the same time, has opened the way to a new concept in TB treatment, proposing a universal regimen that would be equally effective on drug-susceptible and MDR strains [51]. As rifampicin is not part of the regimen, interactions with antiretrovirals are not expected, solving one of the major clinical problems in treating co-infected individuals.

These concept studies have provided the necessary preliminary evidence that the new drugs are effective and basically safe. More information is needed on efficacy, safety and tolerability in MDR/XDR-TB cases. Furthermore, the abovementioned methodology does not allow assignment of adverse events to a particular agent, as the drugs have been studied in combination. Nevertheless, this new scenario allows regulatory authorities to initiate the procedure for a preliminary registration, while additional clinical trials are going on to confirm the results available.

Conclusions

Treatment of pulmonary TB has progressed enormously from the initial monotherapy options offered in the 1940s. While a standard 6-month course of chemotherapy has proved to be extremely effective in treating drug-susceptible TB cases, the appearance of MDR- and XDR-TB has complicated the approach to management of pulmonary TB.

Fortunately, new hopes are generated by the growing evidence that old drugs may still be useful to manage these difficult-to-treat-cases and that new effective and, apparently, well-tolerated drugs are now available.

Caution is necessary to preserve the activity of these new drugs to treat pulmonary TB, as advocated during the 2011 World Health Day on rational use of antibiotics [52], in order to prevent the mistakes that have occurred with the most effective drugs we still have to treat TB (*e.g.* rifampicin and fluoroquinolones) [53]. Today, patients can have the opportunity to benefit from novel drugs and regimens, but it is necessary to administer them in a rational manner, within strengthened health systems, to avoid the real risk of losing their effectiveness in a time shorter than that necessary to develop them. An important contribution to deal with difficult-to-treat forms of TB is represented by the European Respiratory Society/WHO ''Consilium'', a free-access e-consultation platform recently offered to clinicians to support their daily work [54].

Statement of Interest

None declared.

References

1. World Health Organization. Global tuberculosis report 2012. Document WHO/HTM/TB/2012.6. Geneva, World Health Organization, 2012.
2. Migliori GB, Loddenkemper R, Blasi F, *et al.* 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is ''science'' enough to tackle the epidemic? *Eur Respir J* 2007; 29: 423–427.
3. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet* 2006; 367: 952–955.
4. World Health Organization. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO progress report 2011. Document WHO/HTM/TB/2011.3. Geneva, World Health Organization, 2011.
5. Lienhardt C, Glaziou P, Uplekar M, *et al.* Global tuberculosis control: lessons learnt and future prospects. *Nat Rev Microbiol* 2012; 10: 407–416.
6. Raviglione M, Marais B, Floyd K, *et al.* Scaling up interventions to achieve global tuberculosis control: progress and new developments. *Lancet* 2012; 379: 1902–1913.
7. Broekmans JF, Migliori GB, Rieder HL, *et al.* European framework for tuberculosis control and elimination in countries with a low incidence. Recommendations of the World Health Organization (WHO), International Union Against Tuberculosis and Lung Disease (IUATLD) and Royal Netherlands Tuberculosis Association (KNCV) Working Group. *Eur Respir J* 2002; 19: 765–775.
8. Clancy L, Rieder HL, Enarson DA, *et al.* Tuberculosis elimination in the countries of Europe and other industrialized countries. *Eur Respir J* 1991; 4: 1288–1295.
9. Mack U, Migliori GB, Sester M, *et al.* LTBI: latent tuberculosis infection or lasting immune responses to *M. tuberculosis*? A TBNET consensus statement. *Eur Respir J* 2009; 33: 956–973.
10. Laserson KF, Thorpe LE, Leimane V, *et al.* Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; 9: 640–645.
11. World Health Organization. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. Document WHO/HTM/TB/2008.401. Geneva, World Health Organization, 2008.
12. International Statistical Classification of Diseases and Related Health Problems 10th Revision. http://apps.who.int/classifications/icd10/browse/2010/en Date last accessed: March 4, 2013.
13. Migliori GB, Besozzi G, Girardi E, *et al.* Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur Respir J* 2007; 30: 623–626.
14. Sotgiu G, Ferrara G, Matteelli A, *et al.* Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J* 2009; 33: 871–881.
15. Centers for Disease Control and Prevention (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs – worldwide, 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006; 55: 301–305.
16. Fitzgerald D, Haas D. *Mycobacterium tuberculosis. In*: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 6th Edn. Philadelphia, Churchill Livingstone, 2005; pp. 2852–2886.
17. Fighting resistance. Sir John Crofton. *Bull World Health Organ* 2009; 87: 894–895.
18. Yew WW, Lange C, Leung CC. Treatment of tuberculosis: update 2010. *Eur Respir J* 2011; 37: 441–462.
19. Palella FJ Jr, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338: 853–860.
20. Forrest DM, Seminari E, Hogg RS, *et al.* The incidence and spectrum of AIDS-defining illnesses in persons treated with antiretroviral drugs. *Clin Infect Dis* 1998; 27: 1379–1385.
21. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS* 2005; 19: 2109–2116.
22. Gengiah TN, Gray AL, Naidoo K, *et al.* Initiating antiretrovirals during tuberculosis treatment: a drug safety review. *Expert Opin Drug Saf* 2011; 10: 559–574.
23. Decloedt EH, Maartens G, Smith P, *et al.* The safety, effectiveness and concentrations of adjusted lopinavir/ritonavir in HIV-infected adults on rifampicin-based antitubercular therapy. *PLoS One* 2012; 7: e32173.
24. Curran A, Ribera E. HIV and TB coinfection: using adjusted doses of lopinavir/ritonavir with rifampin. *Expert Rev Anti Infect Ther* 2011; 9: 1115–1118.
25. Haas DW, Koletar SL, Laughlin L, *et al.* Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr* 2009; 50: 290–293.
26. Boulle A, Van Cutsem G, Cohen K, *et al.* Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008; 300: 530–539.
27. Wenning LA, Hanley WD, Brainard DM, *et al.* Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother* 2009; 53: 2852–2856.
28. Yost R, Pasquale TR, Sahloff EG. Maraviroc: a coreceptor CCR5 antagonist for management of HIV infection. *Am J Health Syst Pharm* 2009; 66: 715–726.
29. Maartens G, Decloedt E, Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: crucial issues for high-burden countries. *Antivir Ther* 2009; 14: 1039–1043.

30. Bonora S, Di Perri G. Interactions between antiretroviral agents and those used to treat tuberculosis. *Curr Opin HIV AIDS* 2008; 3: 306–312.
31. Toibaro JJ, Losso MH. Pharmacokinetics interaction studies between rifampicin and protease inhibitors: methodological problems. *AIDS* 2008; 22: 2046–2047.
32. Vu DH, Alffenaar JWC, Edelbroek PM, *et al.* Dried blood spots: a new tool for tuberculosis treatment optimization. *Curr Pharm Des* 2011; 17: 2931–2939.
33. Finch CK, Chrisman CR, Baciewicz AM, *et al.* Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* 2002; 162: 985–992.
34. Kenyon C, Wearne N, Burton R, *et al.* The risks of concurrent treatment with tenofovir and aminoglycosides in patients with HIV-associated tuberculosis. *South Afr J HIV Med* 2011; 12: 43–45.
35. World Health Organization. The treatment of tuberculosis guidelines. Document WHO/HTM/TB/2009.420. Geneva, World Health Organization, 2010.
36. Falzon D, Jaramillo E, Schünemann HJ, *et al.* WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; 38: 516–528.
37. Ahuja SD, Ashkin D, Avendano M, *et al.* Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; 9: e1001300.
38. Migliori GB, Sotgiu G, Gandhi NR, *et al.* Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. *Eur Respir J* 2013; 42: 169–179.
39. Falzon D, Gandhi N, Migliori GB, *et al.* Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013; 42: 156–168.
40. Skrahina A, Hurevich H, Zalutskaya A, *et al.* Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J* 2012; 39: 1425–1431.
41. Migliori GB, Centis R, D'Ambrosio L, *et al.* Totally drug-resistant and extremely drug-resistant tuberculosis: the same disease? *Clin Infect Dis* 2012; 54: 1379–1380.
42. Sotgiu G, Centis R, D'Ambrosio L, *et al.* Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; 40: 1430–1442.
43. Lee M, Lee J, Carroll MW, *et al.* Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367: 1508–1518.
44. De Lorenzo S, Alffenaar JW, Sotgiu G, *et al.* Efficacy and safety of meropenem-clavunate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. *Eur Respir J* 2013; 41: 1386–1392.
45. Alsaad N, van Altena R, Pranger AD, *et al.* Evaluation of co-trimoxazole in the treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2013; 42: 504–512.
46. Gler MT, Skripconoka V, Sanchez-Garavito E, *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; 366: 2151–2160.
47. Skripconoka V, Danilovits M, Pehme L, *et al.* Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. *Eur Respir J* 2013; 41: 1393–1400.
48. Diacon AH, Pym A, Grobusch M, *et al.* The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; 360: 2397–2405.
49. Diacon AH, Donald PR, Pym A, *et al.* Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012; 56: 3271–3276.
50. Diacon AH, Dawson R, von Groote-Bidlingmaier F, *et al.* 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; 380: 986–993.
51. Migliori GB, Sotgiu G. Treatment of tuberculosis: have we turned the corner? *Lancet* 2012; 380: 955–957.
52. Raviglione MC, Lange C, Migliori GB. Preventing and managing antimicrobial resistance: imperative for chest physicians. *Eur Respir J* 2011; 37: 978–981.
53. Migliori GB, Langendam MW, D'Ambrosio L, *et al.* Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. *Eur Respir J* 2012; 40: 814–822.
54. Blasi F, Dara M, van der Werf MJ, *et al.* Supporting TB clinicians managing difficult cases: the ERS/WHO Consilium. *Eur Respir J* 2013; 41: 491–494.

Chapter 3

Surgical treatment of pulmonary tuberculosis

Piotr Yablonski[*,#], *Ioan Cordos*[¶], *Eugeny Sokolovich*[*,#], *Nicolas Schönfeld*[+], *Joachim Pfannschmidt*[§] *and Igor Vasilyev*[#]

SUMMARY: Before the introduction of antituberculous drugs, collapse therapy was the dominant surgical treatment for cavitating lung tuberculosis (TB). Today, there is a wide range of indications for surgery in different geographical regions. Most frequently, surgical procedures are indicated for cavernous lesions and tuberculomas in 91.6% of patients, haemoptysis in 58% of patients, and in all patients with multidrug-resistant (MDR) TB. Currently, indications for surgery can be summarised as follows: 1) operations with diagnostic purpose, if it is not possible to rule out TB by other diagnostic methods; 2) elimination of the source of *Mycobacterium tuberculosis* in patients with cavities persisting under chemotherapy (MDR-TB or destroyed lung); 3) tuberculous pleural empyema; and 4) sequelae of past TB. This overview highlights current controversies in different groups of indications in order to facilitate an optimal therapeutic approach in these patients.

*Medical Faculty, State University of St Petersburg, and
[#]St Petersburg State Research Institute of Phtisiopulmonology, St Petersburg, Russia.
[¶]National Institute of Pulmonology, Dept of Thoracic Surgery, Bucharest, Romania.
[+]Dept of Respiratory Medicine, and
[§]Dept of Thoracic Surgery, HELIOS Klinikum Emil von Behring, Lungenklinik Heckeshorn, Berlin, Germany.

Correspondence: P. Yablonski, Ligovsky Ave 4, 191036, St Petersburg, Russia.
Email: glhirurgb2@mail.ru

Eur Respir Monogr 2013; 61: 20–36.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040312
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Tuberculosis (TB) constitutes the eighth most frequent cause of death worldwide, with more than 9 million newly diagnosed patients and more than 1.5 million deaths per year. In 1993, TB was a global threat according to the World Health Organization (WHO), while in 1999 a "Global TB burden" was announced by the WHO. In total, 22 countries were reported as bearing most of the burden (80% of new TB cases worldwide) due to their high TB incidence, making them a major threat for other countries, as countries of origin of TB. According to the WHO, the number of TB patients in Russia constitutes 35.7% of all TB patients in European countries.

The difference in incidence explains why surgical treatment of TB differs across Europe, as do with indications, clinical manifestations requiring surgery and type of operations. As a consequence, the experience and expertise of pulmonologists and thoracic surgeons with surgical treatment of pleuropulmonary TB is different. Due to several factors, most significantly migration and increasing incidence of multidrug-resistant (MDR) TB across Europe, pulmonologists and surgeons are more and more often faced with the need to be familiar with the role and optimal timing for surgery in TB patients. Besides MDR-TB, it has also been suggested that HIV/AIDS may further influence the indications for surgery. However, such an attitude is still not evidence based.

Surgical treatment of pulmonary TB has followed a historical development. Before the widespread use of modern anti-TB drugs, collapse therapy, which induced a decrease in volume of the lung and cavernous lesions within the lung parenchyma, was the predominant form of surgical

treatment. Procedures that did not interfere with the integrity of the thoracic cage were artificial pneumothorax with or without intrapleural pneumolysis, pneumoperitoneum and oleothorax. Additionally, another group of procedures was also in use, which included induced diaphragmatic paralysis or multiple intercostal neurectomy.

Operations that lead to a collapse of the lung by modifying the thoracic cage were thoracoplasty and extrapleural pneumolysis, with plombage as an alternative to thoracoplasty [1–3]. Although these procedures have long been abandoned [4, 5], due to the diversity of clinical forms of the disease and general condition of patients, the need for thoracic cage modifications still exists. This may be the case for patients who cannot undergo pulmonary resection or thoracoplasty, or tolerate medical treatment due to poor general condition, extent of the lung lesions or MDR-TB [6]. However, in the light of modern anti-TB therapy, the need for such an approach is rare.

A first attempt to perform lung resection surgery as a treatment modality for pulmonary TB took place well before modern anti-TB drugs became available. Ruggi was the first to attempt lung resection for TB, in 1884. Tuffier performed pulmonary resection successfully in 1891, but similar procedures were subsequently associated with frequent complications like bronchopleural fistula (BPF), spread of infection, empyema and high mortality. Thus, the widespread use of resectional surgery was delayed until the 1930s and early 1940s. During this period, lobectomy and pneumonectomy were reported, and resectional surgery became preferred. There was an increase in thoracic surgery in general, as well as further development of anti-TB medical treatment. After 1947, with the increasing use of anti-TB drugs, not only the need for surgery but also operative morbidity and mortality decreased.

Collapse therapy did not disappear immediately after introduction of anti-TB drugs, still accounting for treatment of up to 17.7% of pulmonary TB cases, according to reports from the 1960s and early 1970s, with only around 66% being treated by lung resections in the same period. However, by the 1980s and 1990s, lung resections accounted for 92% of the interventions [7]. Although resectional surgery became safer and increased in number with the advent of chemotherapeutic agents, reliance on surgery in the management of TB did not last long. In fact, the use of appropriate chemotherapeutic agents outweighed surgery and a cure was achieved in almost all TB patients [8]. According to data from the early 1990s, fewer than 5% of patients with TB required surgery [9, 10]. However, in the era of MDR-TB, the percentage of patients in whom surgical treatment is indicated has increased to 15% in some countries.

The most common indications for surgery differ throughout the literature, from cavernous lesions and tuberculomas in 91.6% of the patients, through haemoptysis in 58% of patients [9], to MDR-TB as a dominant surgical indication [11]. Currently, bearing in mind these differences, which mostly reflect varying TB prevalence and different clinical forms of the disease depending on the geographical region, the indications for surgery can be summarised as follows: 1) operations with a diagnostic purpose (aimed at establishing the diagnosis when it is impossible to rule out TB by other diagnostic methods); 2) elimination of the source of *Mycobacterium tuberculosis* in patients with cavities persisting under chemotherapy; 3) tuberculous pleural empyema; and 4) sequelae of past TB.

In this chapter, these four categories of indications will be discussed. Additionally, in regions with a high TB prevalence, another disease form may also be seen, characterised by a severe intoxication due to acute progressive lung destruction. This and the localised lesions with high risk of TB activation (mostly tuberculomas) will also be discussed, as they represent further indications for surgery.

Operations with a diagnostic purpose

This type of operation is performed in patients with suspicion of lung cancer or with a lung dissemination or mediastinal lymphadenopathy of unknown origin.

Suspicion of lung cancer

This is one of the most frequent situations for histological diagnosis of TB on surgical specimens. According to several reports, the diagnostic rate exceeds 40% [12]. If the main indication for surgery is presumed malignancy, the discrepancy between the presumed and proven malignancy may be high, for example 34% *versus* 6.25% in a series by FURÁK *et al.* [13]. RIZZI *et al.* [14] reported that lung cancer associated with TB could be confirmed in 26.1% of patients.

An example of a patient subjected to surgery because of a pulmonary nodule of unknown dignity and subsequently confirmed as TB is presented in figure 1. As can be seen on the resected specimen, the lesion is well localised within the lung parenchyma, but a fibro-caseous component is also evident. In addition, resection margins are close to the lesion. In such a situation, anti-TB treatment should be given on the basis of general WHO recommendations on the treatment of pulmonary TB, *i.e.* for 6 months. There is no evidence for an assumption that shorter regimens are similarly sufficient to prevent later relapse. In practice, making the differential diagnosis between TB and lung cancer can be difficult.

Reviewing 36 cases of resected tuberculomas, ISHIDA *et al.* [15] found radiographic criteria of malignancy in 21 (60%) of them. Other differential diagnoses of pulmonary lesions, such as nonspecific lung abscess, collagen vascular disease or pleural effusions of other aetiology, can usually be ruled out by clinical methods less invasive than surgery (bronchoscopy, computed tomography (CT)-guided percutaneous needle biopsy or pleuroscopy) [16]. In order to avoid inappropriate treatment in the form of anti-TB therapy, the following signs on follow-up chest radiographs can be of help: 1) nodular conglomeration in the area of previous tuberculous involvement, 2) recently developed satellite lesions surrounding sequelae of post-primary TB, or 3) parenchymal cavitations in areas where only nodular lesions were previously noted. Pulmonary TB, either active or as a sequela of post-primary TB and treatment, may also coexist with resectable lung cancer. In the pre-operative evaluation of these patients, CT scans and standard radiographs are mandatory to distinguish these lesions.

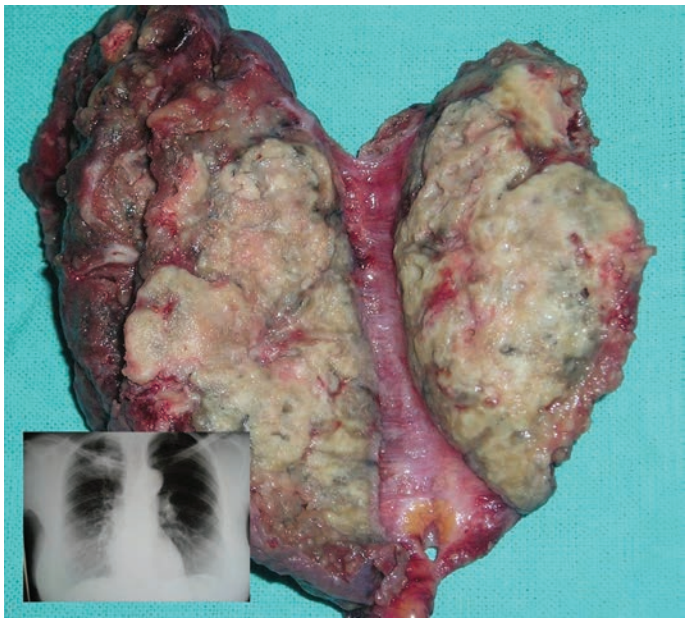


Figure 1. Nodular lesion of unknown origin, subsequently confirmed as tuberculosis. Resected specimen: a tuberculous lesion with a fibro-caseous component, well localised within a lung parenchyma; resection margins are close to the lesion. Detail in inset: pre-operative radiography.

Central localised lung cancer, as presented in figure 2, may be associated with bilateral bullous emphysema and bilateral sequelae of TB. Without the use of CT, at least some of these nodular lesions can be mistakenly diagnosed as metastases. The existence of TB lesions in the nontumour-bearing lobe (as presented) may facilitate the extent of lung resection if the remaining lung parenchyma is functionless.

In some reported series, nearly 90% of patients with scar carcinoma of the lung had stage I disease. This can be partly explained by earlier detection of lung cancer in patients subjected to regular radiological surveillance for their known TB.

Lung dissemination or mediastinal lymphadenopathy of unknown origin

Diffuse lung lesions may be a sign of lung disease, including TB, or of pulmonary manifestation of systemic disorders (connective tissue disease or vasculitis), cardiovascular disorders (pulmonary embolism or congestive heart failure) or occupational pathology (extrinsic allergic alveolitis). As such, they follow the diagnostic algorithms for diffuse lung diseases [17].

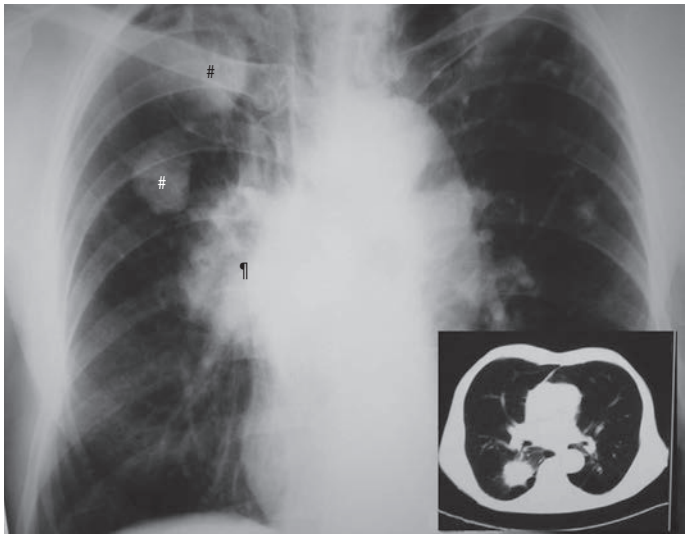


Figure 2. Central lung cancer associated with bilateral bullous emphysema and bilateral tuberculosis sequellae. Inset: computed tomography scan showing right lower lobe cancer. #: specific sequellae; ¶: lung cancer.

The diagnostic value of endobronchial biopsy in tubercular tumours of the bronchial mucosa in diffuse lung lesions varies from 36% to 64%. The diagnostic value of transbronchial lung biopsy is 64–90%, depending on clinical form, level of pathological work-up, duration of the disease and treatment [18]. The presence of epithelioid cell granuloma in biopsies from the lung parenchyma indicates an inflammatory character of diffuse lung disease. Conversely, the similar aspect of sarcoid and TB granulomas, together with inappropriate treatment, is the reason why a reliable morphological diagnosis may be practically impossible in up to 10% of patients.

Clinically, the diagnosis of pulmonary TB is based upon the findings of acid-fast bacteria or *M. tuberculosis* by culture or molecular methods, the typical histology, and a morphological correlate on chest radiograph, CT or by bronchoscopy.

With the advent of endobronchial ultrasound-guided transbronchial needle biopsy, the diagnostic yield of bronchoscopy in the diagnosis of mediastinal lymph node TB has markedly increased [19]. If bronchoscopic biopsies should nevertheless fail to confirm the diagnosis, video-assisted thoracoscopy or mediastinoscopy are further options, in which enlarged mediastinal lymph nodes can be safely biopsied by a cervical mediastinoscopy [20]. In patients with pulmonary nodules of unknown dignity, minimal invasive video-assisted thoracoscopic surgery (VATS) can be indicated to diagnose and treat lesions in TB [21]. However, diagnostic thoracotomy or mediastinotomy are rarely necessary.

Elimination of the source of *M. tuberculosis* in patients with cavities persisting under chemotherapy

The exact incidence of this form of disease is difficult to determine, because a portion of patients with this form are reported under destroyed lung, persistent cavities without specification of the sputum status, or under MDR-TB, although conversion failure may occur for other reasons as well. These persistent sputum-positive patients belong to category II of the WHO, defined as failure of chemotherapy, progression of disease despite chemotherapy, relapse or diagnosis confirmed at the time of surgery for either suspected or unsuspected disease, with or without preoperative chemotherapy [22, 23].

MDR-TB

Recently, MDR-TB has become an important indication for surgery [24, 25]. The success of MDR-TB treatment is between 39% and 79%, *versus* 95% for patients with nonresistant TB [26]. With the emergence of extensively drug-resistant (XDR) TB, adjunctive surgery has become more and more relevant [27].

In general, resection for MDR-TB has two objectives: to cure patients of the disease and to prevent relapse after long-term drug treatment. The rationale for surgical treatment of MDR-TB is threefold. First, the drug resistance profile assumes that there is a high probability of failure or relapse. Secondly, the disease may be localised and amenable to resection, so that most of the radiographically visible disease can be resected. Thirdly, surgery is indicated after sufficient drug treatment to diminish the residual mycobacterial burden and to facilitate healing of the bronchial stump.

Although there are no clear recommendations as to which patients should undergo resection [28], some factors favour adjunctive surgical treatment of MDR-TB: 1) surgery after 18–24 months of multiple-drug anti-TB treatment, 2) surgery in patients with negative smears and cultures, 3) persistent bacterial excretion after an intensive course of anti-TB chemotherapy, and 4) absence of radiological improvement of parenchymal sequelae or drug resistance in sputum-positive patients. In the absence of randomised, controlled studies comparing surgical treatment plus chemotherapy with the efficacy of chemotherapy alone, any significant clinical improvement justifies continuation of antimicrobial therapy. In patients with unchanged or worse clinical, radiological or bacteriological findings, surgery may be offered to the patient as an individual experimental treatment attempt. There are, however, no reliable data on the outcome of these patients after surgery.

Concerning the treatment outcome, according to a meta-analysis, the treatment success rate of pulmonary resection for patients with MDR-TB was 84%, with 6% failure rate, 3% relapse and 5% mortality [29]. Even in XDR-TB, a success rate of 85% was reported. Nevertheless, the authors of this meta-analysis concluded that substantial heterogeneity in the study characteristics prevented a determination of factors associated with a surgical treatment effect additional to combined long-term drug treatment. It is important to note that surgery cannot replace the necessary discipline and adherence to a combined long-term drug treatment, guided by drug susceptibility testing *in vitro* [30].

The appropriate timing of surgery is considered relevant for the treatment outcome, because delayed surgery may favour disease progression and further drug resistance [31]. The inadequacy of second-line treatment agents has been reflected in the MDR-TB mortality rates of 11–37% [32],

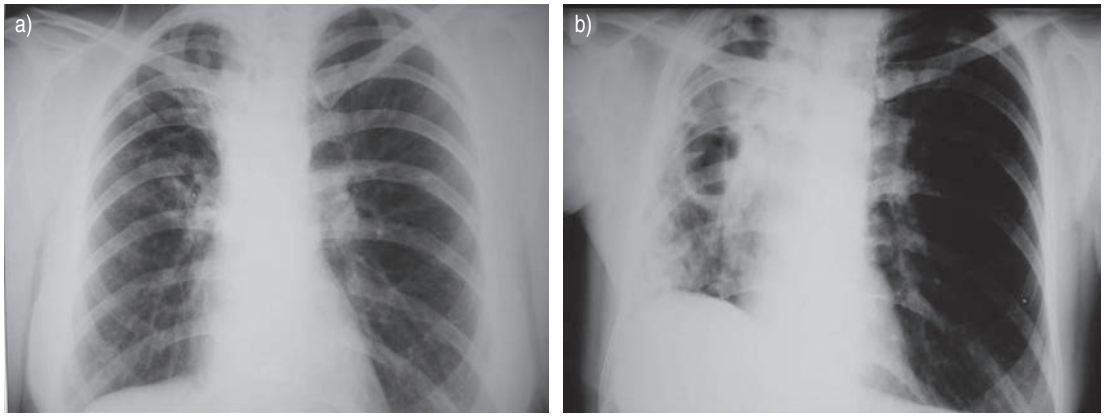


Figure 3. Disease relapse after surgery for multidrug-resistant tuberculosis. a) Radiographic aspect before the first operation (right upper lobectomy), after 2 years of ineffective antituberculosis therapy. b) Radiographic aspect before re-operation (completion pneumonectomy) for tuberculosis relapse, 4 years after the first operation.

yet would not reflect the treatment options in developed countries in Europe and other regions. It was stated by a North American surgical working group that the minimum period for medical treatment before surgery in patients resistant to almost all antibiotics would be at least 3 months [33]. This appears far too short. A longer period of 6–8 months is probably inadequate as well, even in a unilateral involvement, with absence of tubercular bronchitis and radiological improvement of parenchyma sequelae.

Parenchyma-sparing operations should be done whenever possible, because disease relapse may occur despite adequate operation and appropriate medical treatment, as presented in figure 3. Operative morbidity and mortality after resections for MDR-TB according to published data [26, 34–39] are summarised in table 1.

Destroyed lung

The term "destroyed lung" refers to the radiographic aspect of fibrotic cavities combined with caseous lesions, frequently accompanied by sublobar atelectasis or bronchiectasis. Other typical radiographic signs are the upward displacement of the lung hilus, mediastinal shift towards the affected side, and a narrow intercostal space. Most patients with a destroyed lung have a history of re-treatment for TB, with delayed healing or resistance to drugs [40]. About 30% of patients revealed preoperative sputum tests [41].

In patients in whom an adequate anti-TB treatment failed, surgical treatment is recommended if TB-positive sputum, haemoptysis or MDR-TB persists, provided the contralateral lung lesions are stable. In patients with massive haemoptysis of at least 200 $mL \cdot h^{-1}$ and a localised specific lesion that can be identified, embolisation and/or surgery are the ultimate treatment options. However, precise assessment of spread of specific lesions in lung regions other than those causing haemoptysis may be difficult. Moreover, surgery carries a mortality rate of up to 40% when performed as an emergency procedure [42]. In patients with haemoptysis and destroyed lung, delaying surgery may be life threatening.

In areas with a high prevalence of TB, TB is the leading cause of haemoptysis [43–45]. In a recently reported series from South Africa, active TB was a cause of haemoptysis in 65 out of 101 patients [46], whilst in another series, published in 2010, tubercular cavities or destroyed lungs were the source of haemoptysis in 298 out of 645 patients operated for massive recurrent haemoptysis [27].

During the last decades, embolisation has become the preferred treatment option for haemoptysis [47]. If embolisation of bronchial arteries is not possible for any reason, emergency thoracotomy is indicated [48]. The risk of complications after embolisation is low, with immediate control of bleeding in 75–94% of patients. However, it has been shown that recurrent bleeding after initial embolisation occurs in 18–42%, with high associated mortality [49–52].

Table 1. Operative morbidity and mortality in patients with multidrug-resistant tuberculosis

First author [ref.]	Period	Patients	Lobectomy	Pneumonectomy	Segmental resection	Other	Operative morbidity %	Operative mortality %
MAN [34]	1995–2005	45	30		4	11	11.1	
KIR [35]	1993–2005	81	37	39	1	4	20.9	2.5
SHIRAISHI [36]	2000–2007	56	33	22	1		16	0
MOHSEN [37]	1999–2005	23	12	11			34.7	4.3
KANG [38]	1996–2008	72	38	23	10	1	11	1.3
WANG [39]	1995–2006	56	31	25			25	0
VAN LEUVEN [26]	1990–1995	62	26	35	1		23	1.6

In a single-centre study published in 2007, four risk factors were identified for recurrence following successful embolisation for life-threatening haemoptysis: 1) lack of complete cessation of haemoptysis within 7 days of embolisation, 2) need for blood transfusion, 3) presence of aspergilloma, and 4) absence of active TB [53]. A risk score for massive re-bleeding or death was developed based on these four criteria, which predicted that patients at low risk (0 or 1 risk factor) had a 10% chance of a nonfatal re-bleeding, whereas patients at high risk (2 to 4 risk factors), had a 73% chance of re-bleeding and a 31% mortality rate.

In a series of 38 patients with destroyed lungs combined with aspergilloma and haemoptysis who underwent pneumonectomy or pleuropneumonectomy, one out of seven patients with post-operative empyema died [54]. In another series, all 13 patients with TB and massive haemoptysis were cured by emergency thoracotomy [41].

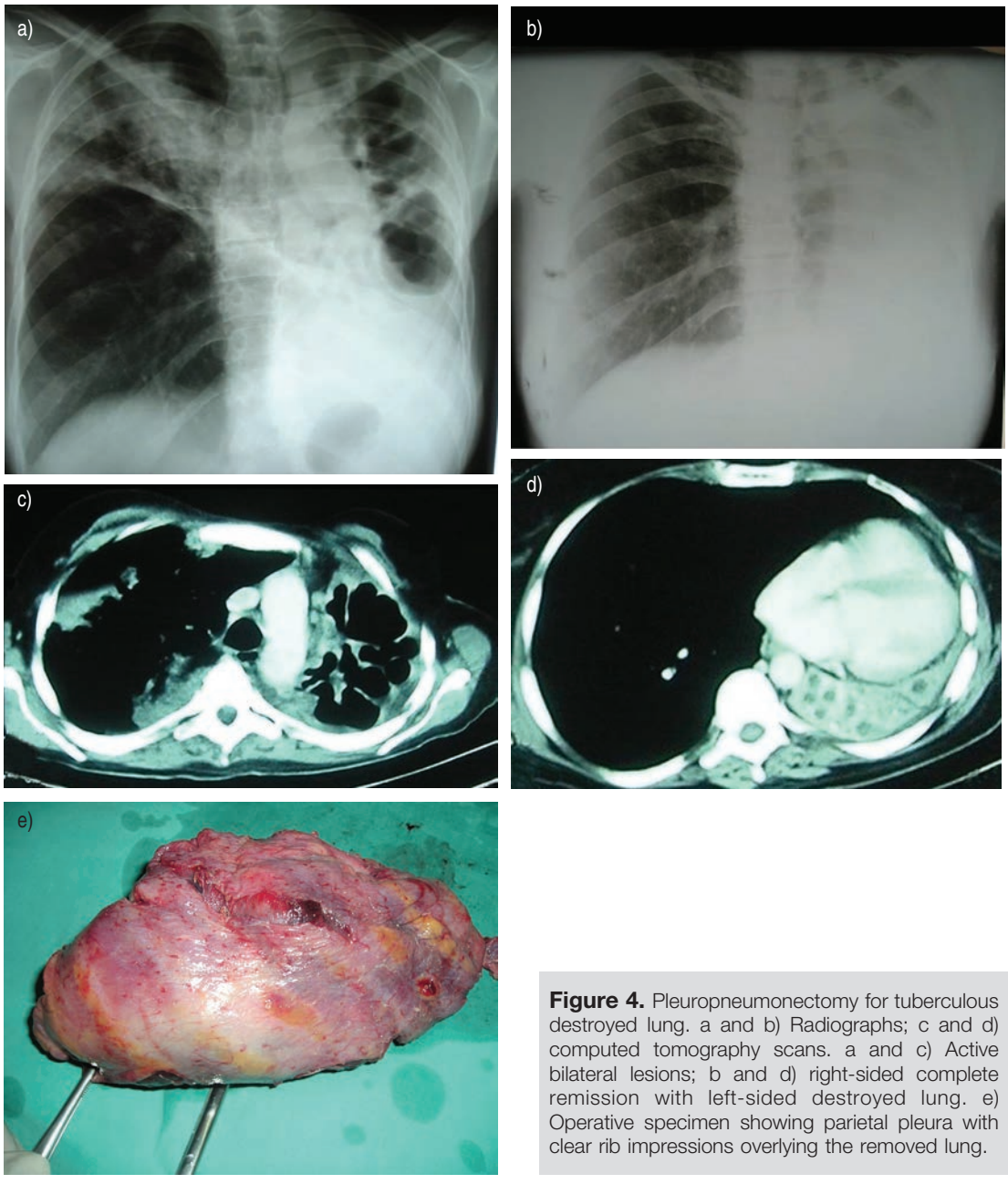


Figure 4. Pleuropneumonectomy for tuberculous destroyed lung. a and b) Radiographs; c and d) computed tomography scans. a and c) Active bilateral lesions; b and d) right-sided complete remission with left-sided destroyed lung. e) Operative specimen showing parietal pleura with clear rib impressions overlying the removed lung.

Bronchial stenosis, reported in about 18% of patients with post-primary TB, can be seen as a result from healing of endobronchial TB, and is often combined with a destroyed lung. This entity should be clearly distinguished from an active TB infection within the bronchus [55]. If present, stenosis of the main bronchus is not an obstacle for pneumonectomy in these patients. In order to resect a destroyed lung, extrapleural pneumonectomy is the only possible operation in many patients, as presented in figure 4.

In patients with destroyed lung complicated by empyema, especially if a BPF exists, conservative treatment with thoracic drainage is advocated as an initial procedure in all patients. Surgical resection in these patients is challenging and may only be attempted after control of the mycobacterial infection. However, in the absence of BPF, surgery may be an acceptable option, as for example reported in a series of 24 patients with pre-operative empyema, in whom 22 pleuropneumonectomies and two conventional pneumonectomies were performed, with no operative mortality. Post-operative empyema developed in eight (33%) out of 24 patients who had empyema pre-operatively, and in seven (10%) out of 70 who did not have pre-operative empyema [56]. Alternative procedures, like, decortication, and thoracomyoplasty, have also been reported, but they are not an acceptable option in the majority of clinical situations [57].

Tuberculous pleural empyema

Owing to the diffuse pleural involvement and high diagnostic accuracy of pleural biopsy (accuracy >60%, even more with cultures of tissue samples) and thoracoscopy (99–100% sensitivity), most patients with pleural TB are not candidates for open surgery. Thoracotomy comes into consideration only in patients in whom conventional diagnosis fails and is definitely indicated in patients with specific pleural empyema.

There are two main determinants of the therapeutic approach in these patients: 1) presence or absence of typical radiographic signs of TB, and 2) presence or absence of BPF. In many patients without radiographic signs of pulmonary TB, the diagnosis of the specific pleuritis is obtained only after histopatholgical analysis of the removed pleura specimen. This means that the appropriate thoracoscopic diagnosis was omitted in patients who presented either with a radiographic aspect of trapped lung, when conventional diagnosis is not possible (fig. 5), or with the radiographic aspect of pleural effusion or hydropneumothorax, when the appropriate diagnosis was possible but not performed (fig. 6).

If a pleural empyema exists in the presence of radiographic signs of lung TB, conservative treatment in form of prolonged chest tube aspiration is the definitive treatment in the great majority of patients. In these patients, surgical treatment comes into consideration in those who have received a few weeks of anti-TB medication prior to pleural surgery to achieve sputum conversion and to reduce TB-related complications. Although several reports have confirmed the value of VATS [58, 59], the open approach is still necessary for the majority of patients.

Figure 5. Specific empyema with a radiographic aspect of trapped lung. Radiograph on admission. Pre-operative exploration of the pleural space was impossible, but pleural tuberculosis was confirmed by the analysis of the pleural peel removed during decortication.

If a BPF exists, surgical treatment is rarely indicated. Although immediate open drainage is advocated by some authors, tube thoracostomy is the most frequently used initial treatment option. Open thoracostomy (Eloesser window) is reserved for severely ill patients with high operative risks, because it may jeopardise subsequent decortication. However, García-Yuste *et al.* [60] suggest that a two-stage management with open

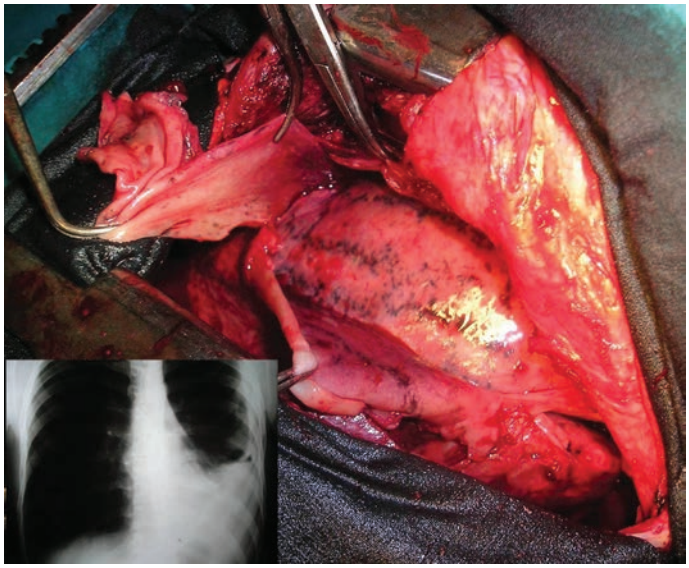


Figure 6. Specific empyema. Main image shows operative view with a pleural peel over the lung unaffected by tuberculosis. Inset: radiographic aspect after pleural drainage for hydropneumothorax as initial manifestation of the disease.

thoracostomy and subsequent muscle plombage of the cleaned residual space is a reasonable alternative in cases unsuitable for decortication. Poor general condition and extensive calcifications precluding decortication are indications for this type of treatment.

Due to interstitial fibrosis, damage of lung parenchyma or chronic pleuritis caused by TB, lung compliance and lung volume are frequently reduced. After lung resection, re-expansion of such affected lungs is compromised and significant residual pleural space remains. This facilitates the development of subsequent post-operative empyema. The main problem in these patients is the uncertainty in pre-operative functional evaluation. When lung resection is inevitable during the operation, even pneumonectomies for destroyed lung can be considered. However, several reports argue that previous TB and coexistent empyema represent significant risk factors for procedure-related morbidity and mortality [60, 61] and they preclude resectional surgery.

The data in the literature raise some concern relating to the decision-making process in patients with chronic specific empyema and collapsed lung. Suggestions that a pneumonectomy could be deliberately done in patients with a lung perfusion of the affected lung that is less than 15%, assuming the parenchyma is irreversibly damaged [62], should not be automatically applied in these patients. A low perfusion rate is not necessarily an indication of functionless tissue: some reports have even shown increased perfusion after decortication [63]. It was recently reported that preservation of the lung may be superior to lung resection, both for pleural infection control and avoidance of potential problems after lung resection [64]. It should be born in mind that any lung resection with concomitant empyema, especially pneumonectomy, is associated with high morbidity and mortality, even in experienced hands. It often seems appropriate to preserve the lung regardless of its functional status, serving as prosthesis, rather than to remove the lung, unless parenchymal lesions are life threatening for the patient [65, 66].

A prolonged air leak after decortication usually stops with prolonged drainage. In order to avoid persisting pleural spaces due to incomplete lung re-expansion after decortication or lung resection, muscle plombage or thoracoplasty can be performed as preventive measures. Thoracoplasty, despite its unwarranted bad reputation, should still be available in the surgeon's armamentarium and can be a helpful adjunct in patients with marked malnutrition. It was demonstrated that a four-rib thoracoplasty, with a stable and retracted mediastinum, may be expeditiously carried out [67], compared with the preparation and transfer of two or three muscle flaps.

Surgery for sequelae of TB

Bronchiectasis

Post-tuberculous bronchiectasis is relatively common in patients with a history of TB relapses. This condition itself is not an absolute indication for operation, but in these patients, a relatively

high incidence of symptoms may exist, mostly haemoptysis, recurring pneumonia and abscess formation. Sputum may be persistently positive for *M. tuberculosis*. Post-tuberculous bronchiectasis is often associated with bronchostenosis, atelectasis and large areas of residual fibro-nodular disease.

When bronchiectasis is located in poor drainage areas of the lungs, such as lower lobes, middle lobe or lingula, resection may be necessary. Surgery by minimal invasive techniques is usually recommended for younger patients with moderate-to-severe bronchiectasis representing the only visible residues of a previous specific process [68, 69]. Long-term results are encouraging, with 60–75% of patients becoming symptom free and a low mortality of 0–1.7% [70].

Tuberculous bronchial stenosis

Tuberculous bronchial stenosis is a serious clinical problem, because it can cause pneumonia, wheezing and dyspnoea on exertion. Surgical resection with bronchoplastic reconstruction has long been the standard treatment [71, 72]. However, a variety of interventional bronchoscopic techniques have been developed, such as stents, laser resections, argon plasma coagulation, balloon dilatation or cryotherapy, which are now being performed with increasing frequency [73, 74].

Further indications for surgery

Apart from the above-mentioned disease forms, surgery comes into consideration in an additional two groups of patients: in patients with localised lesions with high risk of TB activation (mostly tuberculoma), and in patients with rare, rapidly progressive disease forms with intoxication and lung destruction.

Tuberculoma

In resected tuberculomas, *M. tuberculosis* is found in around 85% of cases. The capsule surrounding the caseous necrosis interferes with the penetration of chemotherapeutics into the centre of infection or reduces their concentration. Thus, the reported exacerbation rate is 54.7% even after 6 months of controlled chemotherapy, and can be as high as 81.5% after shorter courses of therapy. Timely resection of tuberculoma prevents progression of the TB infection, reduces the duration of treatment, and allows complete clinical, social and professional rehabilitation.

However, during the early period of treatment, a tuberculoma may increase in size, thus making clinical decisions more difficult. The overall tuberculoma progression rate is approximately 13%. Progression occurs in 5.8% of patients in the presence of tuberculomas of size <2 cm, and in 14.8% and 25% of patients in the presence of tuberculoma of diameter <4 cm and >4 cm, respectively [75]. Single pulmonary nodules containing both TB and malignancy have been reported. There is also a possibility of misdiagnosis of malignancy for tuberculoma. Thus, the dynamics of tuberculoma size alone is not a reliable criterion for clinical use. This justifies a surgical approach to all tuberculomas, regardless of size.

The operations of choice in these patients are atypical and typical mono- and bi-segmental resections. Lobectomy may be necessary only for large tuberculomas or for those localised near the lung hilum. Frozen section is always necessary, not only if malignancy is suspected.

Rare forms of the disease

Acute progressive lung destruction with severe intoxication is not sufficiently addressed in the literature. Most of the knowledge about it is owing to rare reports from the regions with a high prevalence of TB. In a series of 153 patients who underwent a lung resection for a destructive form of lung TB, surgery was indicated in the early phase of the disease in 43.9% of patients, because of the failure of medical treatment to stop the rapidly progressive deterioration. In 9.8% and 12.5%

of patients, the duration of medical treatment before surgery was 2 months and 2–4 months, respectively [76].

Lung resection may sometimes be indicated even during the acute stage of disease with rapidly progressing caseous pneumonia. The course of the disease is usually characterised by the acute onset, high febrility (39–40°C), severe fatigue, dyspnoea, tachycardia, night sweats and cough, initially dry and persistent, soon becoming productive (up to 200–500 $mL \cdot day^{-1}$). Haemoptysis may exist, especially if a vessel wall is close to the area of the lung destruction. The patients waste progressively. A rapidly progressing caseous necrosis exists without a tendency towards localisation, leading to severe immunodeficiency and rapid and massive bacterial proliferation. Clinical improvement can be rarely achieved despite complex intensive therapy. The only appropriate option in such a situation is a lung resection, lobectomy and bilobectomy, less frequently pneumonectomy. It is a high risk procedure, but also the only one giving some chances for survival of these patients.

The number of new cases with a rapidly progressing destruction (or caseous pneumonia) has increased from 3.3% to 6.7% over the past 15 years. Patients with significant hypoproteinaemia, who are on corticosteroid or cytostatic therapy, constitute a high-risk group in terms of developing rapidly progressing destruction from any form of TB infection. In around two-thirds of cases, nonspecific pathogenic bacteria are also isolated. Prognosis in cases of rapidly progressing destruction with severe intoxication is unfavourable: during the first month, 15–38.5% of patients die. Overall mortality in this group is higher than 70%. Hence, surgical interventions in these patients represent a life-saving procedure [77–80].

Contraindications for surgery in patients with pulmonary TB

General contraindications, related to general and functional limitations for lung resection, do not differ from contraindications for thoracic surgery in the presence of any other pathology. However, in patients with borderline values of predicted post-operative pulmonary function parameters, care should be taken of the decreased lung compliance due to chronic inflammatory disease and higher probability of post-operative air leak than in patients with non-TB pathology. Most importantly, resection margins have to be clear of disease and have normal lung parenchyma.

Detailed bronchoscopic exploration is mandatory, including biopsies from the anticipated suture line and from sites with suspected active disease. Contraindication for surgery depends on the endoscopic finding of tuberculous bronchitis, because endobronchial granulation tissue, erosion and ulceration of the mucosa may predispose to the development of BPF [81].

Surgical procedures for pulmonary TB

Thoracic surgery as part of a TB treatment concept includes the whole range of thoracic procedures: atypical resections, subsegmental resections, (bi)segmentectomy, (bi)lobectomy, pneumonectomy (including intrapericardially and extended pneumonectomies), lung decortication and pleurectomy. In a situation characterised by an increased number of patients with bilateral advanced lung destruction and MDR-TB, one-stage and multiple-stage bilateral lung resections, including operations on a single lung after contralateral pneumonectomy, gain importance.

Segment/wedge resections

This type of operation constitutes approximately 30% of all resectional procedures. The indications for segmental resections are tuberculomas and small cavities most frequently located in the intersegmental boundaries between two segments. The mortality after segmentectomy is reported as less than 1% and the rate of full recovery from TB is as high as 95–97%. The average

length of a post-operative hospital stay in patients undergoing wedge resection or segmentectomy is reported to be 7–10 days [82, 83].

One of the features of these operations is the difficulty in defining the demarcation between the boundaries of the segment being resected. To achieve this, the following method is used: the ventilation of the lung being operated is restored and at the same time the bronchus of the segment to be resected is clamped. From a technical point of view it is important to dissect along the plane of intersegmental fissures, preserving the venous network on the surface of the remaining segments, while performing an anatomical resection with separate handling of hilum elements of the resected segment. This technical element of the anatomical segmentectomy is necessary for prevention of venous thrombosis in the remaining segments. The technique described above is considered classical. Under these circumstances one should be aware of any uncritical use of stapling devices, especially in case of MDR-TB. Unrecognised TB foci entrapped with the stapler line during non-anatomical lung resections increase the risk of TB reactivation and contamination of the pleural cavity.

Lobectomy

Lobectomy and bilobectomy constitute up to 41.6% of all lung resections in some institutions (M. Kobak, St Petersburg State Research Institute of Phtisiopulmonology, St Petersburg, Russia; personal communication). The indication for lobectomy is tuberculous lung destruction located within the boundaries of a single lobe.

Mortality after lobectomy for the sequelae of TB is between 2% and 3% and the average post-operative hospital stay is 2–3 weeks. The anatomical nature of this operation lies in a separate handling of the hilum elements, division of the interlobar fissures and removal of the regional bronchopulmonary lymph nodes. In order to prevent any unintended opening of subpleural cavities, extrapleural resection should be used freely but limited to the areas with dense pleural adhesions.

Sclerosed and calcified lymph nodes can be the cause of technical difficulties during the separation of bronchi and vessels, so meticulous dissection techniques are required. The removal of lymph nodes is justified to facilitate the dissection of the hilum elements only. Complications, like lung lacerations or opening of a pleural cavitation, are often related to difficulties during the lysis of pleural adhesions.

The immediate results depend on the type of lobectomy: full recovery is reported in 85–95% of patients, with a mortality of 0.3–11%, depending on the type of lesions and publication period. Working capacity is restored 2–3 months after the operation [84].

Pneumonectomy

Among lung resections for TB, pneumonectomy and pleuropneumonectomy constitute around 12–15%, in some institutions reaching 30–40% in patients with MDR-TB (M. Kobak, St Petersburg State Research Institute of Phtisiopulmonology; personal communication). Pneumonectomy is indicated in patients with destroyed lung of TB and secondary irreversible changes in six or more segments of the lung. Taking into consideration the complexity and traumatic nature of pneumonectomy in TB patients with extensive severe fibrous changes of the lungs, this operation has to be considered as a high-risk procedure. Separate ligation of the hilum vessels and reinforcement by suturing is recommended in all cases.

Extrapleural freeing of the lung is advised in case of severe pleuropulmonary adhesions, in order to prevent tears of the lung tissue and opening of the cavities leading to massive contamination of the pleural space. Most importantly, procedures of bronchial stump coverage should be performed. Flaps from mediastinal pleura, muscles or omental pedicle wrap can be used to protect the bronchus. Pneumonectomy and pleuropneumonectomy are characterised by high efficacy (95%)

and a mortality rate of 3.5%. The main causes of lethal outcomes are systemic complications due to comorbidities and limited functional reserves.

Completion pleuropneumonectomy is frequently performed as repeat thoracotomies in case of post-operative recurrences or pleuropulmonary complications in the presence of disease progression with massive bacterial invasion by MDR-TB. The operation is performed in one stage or multiple stages, when prior debridement of the empyema cavity is required. The post-operative period is reported uneventful in 71% of patients, with a mortality rate of 6.6% from pleuropulmonary complications and of 4.1% from systemic complications. The most significant post-operative complications are pleural empyema, bronchial fistulae and TB recurrence in the contralateral lung. The frequency of these complications depends on the clinical course of the disease and type of operation [85, 86].

Thoracoplasty

Extrapleural thoracoplasty

Thoracoplasty was historically introduced as a method to merge the thoracic wall with the underlying lung. The procedure lost its leading role in the surgical treatment concept of TB after methods of resectional surgery progressed. However, the pathogenetic rationale of thoracoplasty is reduction of the lung volume of the corresponding hemithorax after rib resection and, hence, elastic recoil of the lung in general and in affected areas in particular are reduced.

Favourable conditions for cavernous collapse are created by mobilising the external chest wall. Although thoracoplasty is regarded as a historic procedure, today's indication can be seen to be highly individualised. This is a painful and disfiguring operation, but it may still have a small place in post-resectional residual spaces, such as in patients with single caverns that have a thin wall. Thoracoplasty is performed in one stage with a subperiosteal resection of the posterior portions of the upper five to seven ribs. One or two ribs below the lower border of the cavern are always resected. In case of large upper lobe caverns, the upper two or three ribs should be resected completely, as shown in figure 7. In order to maintain lung collapse and to prevent a free-floating chest wall, a pressure bandage is applied for 1.5–2 months after the operation.

The most frequent complications are specific and nonspecific pneumonia and atelectasis. Currently, the efficacy of thoracoplasty as a separate procedure in case of MDR-TB does not exceed 25% [87, 88].

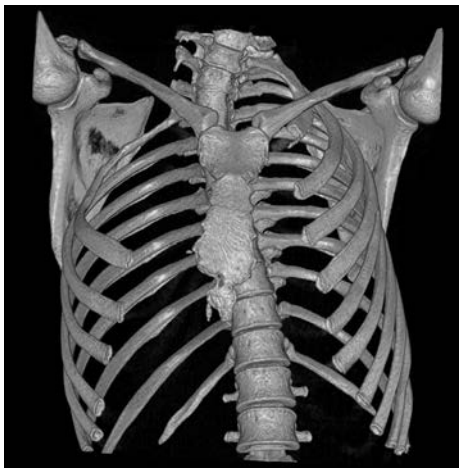


Figure 7. Computed tomography scan of a patient after thoracoplasty. Three-dimensional reconstruction of a patient after right-sided thoracoplasty, with three upper ribs removed.

Osteoplastic thoracoplasty

Osteoplastic thoracoplasty is preferred over extrapleural thoracoplasty due to its better cosmetic results. As for thoracoplasties in general, indications are highly individualised: in a small subgroup of patients, osteoplastic thoracoplasties may be beneficial for single or multiple caverns in the upper lobe and apical segment of the lower lobe of a single or both lungs, during a stage of relative stabilisation.

Osteoplastic thoracoplasty makes it possible to reach the maximal rib mobility and to form a ''new'' pleural dome at the lower level after extended lung resection or in case of caverns localised in anterior regions of the upper lobe of the lung. The congruence and affinity of the lung and chest wall is thus achieved. Potential advantages of osteoplastic thoracoplasty include lesser trauma, the absence of an apparent chest wall deformity, and the absence of a floating chest wall, which makes pressure bandages redundant.

Conclusion

Pulmonary TB remains a global healthcare problem and is becoming increasingly important. Thoracic surgery continues to play an important but highly selective role in the complex treatment of the sequelae, complications and cure of pulmonary TB. Today's surgeons should be familiar with the interdisciplinary management of MDR-/XDR-TB, because in selected cases surgical investigation or intervention may be required. A revision of old principles of surgical treatment and their adaptation to modern evidence-based medicine is necessary, demanding more multicentre international studies.

Statement of Interest

None declared.

References

1. Povah AH. Thoracoplasty with temporary extraperiosteal lucite ball plombage. *J Thorac Surg* 1953; 25: 516–523.
2. Rosu P, Zitti E, Rusdea N, *et al.* Considerations regarding thoracoplasty with temporary or permanent lucite ball plombage. *Ftiziologia* 1956; 4: 333–341.
3. Ivancenco O, Buzescu M. The role of thoracoplasty in treating pulmonary tuberculosis in children and young adults. *Ftiziologia* 1952; 3: 52–55.
4. Thomas GE, Chandrasekhar B, Grannis FW Jr. Surgical treatment of complications 45 years after extraperiosteal pneumolysis and plombage using acrylic resin balls for cavitary pulmonary tuberculosis. *Chest* 1995; 108: 1163–1164.
5. Uchida T, Wada M, Sakamoto J. Developing bronchial fistulas as a late complication of extraperiosteal plombage. *Jpn J Thorac Cardiovasc Surg* 1999; 47: 214–217.
6. Jouveshomme S, Dantzenberg B, Bakdach H, *et al.* Preliminary results of collapse therapy with plombage for pulmonary disease caused by multidrug-resistant mycobacteria. *Am J Respir Crit Care Med* 1998; 157: 1609–1615.
7. Neptune WB, Kim S, Bookwalter J. Current surgical management of pulmonary tuberculosis. *J Thorac Cardiovasc Surg* 1970; 60: 384–391.
8. Langston H, Barker W, Pyle M. Surgery in pulmonary tuberculosis. 11 year review of indications and results. *Ann Surg* 1966; 164: 567–573.
9. Reed CE, Parker EF, Crawford FA Jr. Surgical resection for complications of pulmonary tuberculosis. *Ann Thorac Surg* 1989; 48: 165–167.
10. Moran JF. Surgical treatment of pulmonary tuberculosis. *In*: Sabiston DC, Spencer FC, eds. Surgery of the Chest. 6th Edn. Philadelphia, Saunders, 1995; pp. 752–772.
11. Treasure RL, Seaworth BJ. Current role of surgery in mycobacterium tuberculosis. *Ann Thorac Surg* 1995; 59: 1405–1409.
12. Mouroux J, Maalouf J, Padovani B, *et al.* Surgical management of pleuropulmonary tuberculosis. *J Thorac Cardiovasc Surg* 1996; 111: 662–670.
13. Furák J, Troján I, Szöke T, *et al.* Surgical intervention for pulmonary tuberculosis: analysis of indications and perioperative data relating to diagnostic and therapeutic resections. *Eur J Cardiothorac Surg* 2001; 20: 722–727.
14. Rizzi A, Rocco G, Robustellini M, *et al.* Results of surgical management of tuberculosis: experience in 206 patients undergoing operation. *Ann Thorac Surg* 1995; 59: 896–900.
15. Ishida T, Yokoyama H, Kaneko S, *et al.* Pulmonary tuberculoma and indications for surgery: radiographic and clinicopathological analysis. *Respir Med* 1992; 86: 431–436.
16. Ost DE, Gould MK. Decision making in patients with pulmonary nodules. *Am J Respir Crit Care Med* 2012; 185: 363–372.
17. Ensminger SA, Prakash UB. Is bronchoscopic lung biopsy helpful in the managements of patients with diffuse lung disease? *Eur Respir J* 2006; 28: 1081–1084.
18. Chung HS, Lee JH. Bronchoscopic assesment of the evolution of endobronchial tuberculosis. *Chest* 2000; 117: 385–389.
19. Medford AR, Bennett JA, Free CM, *et al.* Endobronchial ultrasound guided transbronchial needle aspiration. *Postgrad Med J* 2010; 86: 106–115.
20. Porte H, Roumilhac D, Eraldi L, *et al.* The role of mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. *Eur J Cardiothorac Surg* 1998; 13: 196–199.
21. Hsu KY, Lee HC, Ou CC, *et al.* Value of video-assisted thoracoscopic surgery in the diagnosis and treatment of pulmonary tuberculoma: 53 cases analysis and review of the literature. *J Zhejiang Univ Sci B* 2009; 10: 375–379.

22. Mehran RJ, Deslauriers J. Tuberculosis and atypical mycobacterial disease. *In*: Pearson FG, Coper JD, Deslauriers J, *et al.*, eds. Thoracic Surgery. 2nd Edn. New York, Churchill Livingstone, 2002; pp. 547–576.
23. Naidoo R. Active pulmonary tuberculosis: experience with resection in 106 cases. *Asian Cardiovasc Thorac Ann* 2007; 15: 134–138.
24. Olcmen A, Gunluoglu MZ, Demir A, *et al.* Role and outcome of surgery for pulmonary tuberculosis. *Asian Cardiovasc Thorac Ann* 2006; 14: 363–366.
25. Johnston JC, Shahidi NC, Sadatsafavi M, *et al.* Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS One* 2009; 4: e6914.
26. van Leuven M, De Groot M, Shean KP, *et al.* Pulmonary resection as an adjunct in the treatment of multiple drug-resistant tuberculosis. *Ann Thorac Surg* 1997; 63: 1368–1372.
27. Dewan RK. Surgery for pulmonary tuberculosis – a 15-year experience. *Eur J Cardiothorac Surg* 2010; 37: 473–477.
28. Sung SW, Kang CH, Kim YT, *et al.* Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. *Eur J Cardiothorac Surg* 1999; 16: 187–193.
29. Xu HB, Jiang RH, Li L. Pulmonary resection for patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *J Antimicrob Chemother* 2011; 66: 1687–1695.
30. Simons SO, van Soolingen D. Drug susceptibility testing for optimizing tuberculosis treatment. *Curr Pharm Des* 2011; 17: 2863–2874.
31. Marrone M, Venkataramanan V, Goodman M, *et al.* Surgical interventions for treating multidrug and extensively-drug resistant pulmonary tuberculosis. *Cochrane Database Syst Rev* 2011; 2: CD009010.
32. Pomerantz M, Madsen L, Goble M, *et al.* Surgical management of resistant mycobacterial tuberculosis and other mycobacterial pulmonary infections. *Ann Thorac Surg* 1991; 52: 1108–1111.
33. Pomerantz BJ, Cleveland JC Jr, Olsen HK, *et al.* Pulmonary resection for multi-drug resistant tuberculosis. *J Thorac Cardiovasc Surg* 2001; 121: 448–453.
34. Man MA, Nicolau D. Surgical treatment to increase the success rate of multidrug-resistant tuberculosis. *Eur J Cardiothorac Surg* 2012; 42: e9–e12.
35. Kir A, Inci I, Torun T, *et al.* Adjuvant resectional surgery improves cure rates in multidrug-resistant tuberculosis. *J Thorac Cardiovasc Surg* 2006; 131: 693–696.
36. Shiraishi Y, Katsuragi N, Kita H, *et al.* Aggressive surgical treatment of multidrug-resistant tuberculosis. *J Thorac Cardiovasc Surg* 2009; 138: 1180–1184.
37. Mohsen T, Zeid AA, Haj-Yahia S. Lobectomy or pneumonectomy for multidrug-resistant pulmonary tuberculosis can be performed with acceptable morbidity and mortality: a seven-year review of a single institution's experience. *J Thorac Cardiovasc Surg* 2007; 134: 194–198.
38. Kang MW, Kim HK, Choi YS, *et al.* Surgical treatment for multidrug-resistant and extensive drug-resistant tuberculosis. *Ann Thorac Surg* 2010; 89: 1597–1602.
39. Wang H, Lin H, Jiang G. Pulmonary resection in the treatment of multidrug-resistant tuberculosis: a retrospective study of 56 cases. *Ann Thorac Surg* 2008; 86: 1640–1645.
40. Park SK, Kim JH, Kang H, *et al.* Pulmonary resection combined with isoniazid- and rifampin-based drug therapy for patients with multidrug-resistant and extensively drug-resistant tuberculosis. *Int J Infect Dis* 2009; 13: 170–175.
41. Bai L, Hong Z, Gong C, *et al.* Surgical treatment efficacy in 172 cases of tuberculosis-destroyed lungs. *Eur J Cardiothorac Surg* 2012; 41: 335–340.
42. Fernando HC, Stein M, Benfield JR, *et al.* Role of bronchial artery embolization in the management of hemoptysis. *Arch Surg* 1998; 133: 862–866.
43. Ozgul MA, Turna A, Yildiz P, *et al.* Risk factors and recurrence patterns in 203 patients with hemoptysis. *Tuberk Toraks* 2006; 54: 243–248.
44. Kim YG, Yoon HK, Ko GY, *et al.* Long-term effect of bronchial artery embolization in Korean patients with haemoptysis. *Respirology* 2006; 11: 776–781.
45. Knott-Craig CJ, Oostuizen JG, Rossouw G, *et al.* Management and prognosis of massive hemoptysis. Recent experience with 120 patients. *J Thorac Cardiovasc Surg* 1993; 105: 394–397.
46. Gross AM, Diacon AH, van den Heuvel MM, *et al.* Management of life-threatening haemoptysis in an area of high tuberculosis incidence. *Int J Tuberc Lung Dis* 2009; 13: 875–880.
47. Andréjak C, Parrot A, Bazelly B. Surgical lung resection for severe hemoptysis. *Ann Thorac Surg* 2009; 88: 1556–1565.
48. Erdogan A, Yegin A, Gurses G, *et al.* Surgical management of tuberculosis-related hemoptysis. *Ann Thorac Surg* 2005; 79: 299–302.
49. Kato A, Kudo S, Matsumoto K, *et al.* Bronchial artery embolization for hemoptysis due to benign diseases: immediate and long-term results. *Cardiovasc Intervent Radiol* 2000; 23: 351–357.
50. Osaki S, Nakanishi Y, Wataya H, *et al.* Prognosis of bronchial artery embolization in the management of hemoptysis. *Respiration* 2000; 67: 412–416.
51. Uflacker R, Kaemmerer A, Neves C, *et al.* Management of massive hemoptysis by bronchial artery embolization. *Radiology* 1983; 146: 627–634.

52. Swanson KL, Johnson CM, Prakash UB, *et al.* Bronchial artery embolization: experience with 54 patients. *Chest* 2002; 121: 789–795.
53. Van den Heuvel MM, Els Z, Koegelenberg CF, *et al.* Risk factors for recurrence of haemoptysis following bronchial artery embolisation for life-threatening haemoptysis. *Int J Tuberc Lung Dis* 2007; 11: 909–914.
54. Souilamas R, Riquet M, Barthes FP, *et al.* Surgical treatment of active and sequelar forms of pulmonary tuberculosis. *Ann Thorac Surg* 2001; 71: 443–447.
55. Williams DJ, York EL, Nobert EJ, *et al.* Endobronchial tuberculosis presenting as asthma. *Chest* 1988; 93: 836–838.
56. Kim YT, Kim HK, Sung SW, *et al.* Long-term outcomes and risk factor analysis after pneumonectomy for active and sequela forms of pulmonary tuberculosis. *Eur J Cardiothorac Surg* 2003; 23: 833–839.
57. Massard G, Rouge C, Wihlm JM, *et al.* Decortication is a valuable option for late empyema after collapse therapy. *Ann Thorac Surg* 1995; 60: 888–895.
58. Kim YI, Goo JM, Kim HY, *et al.* Coexisting bronchogenic carcinoma and pulmonary tuberculosis in the same lobe: radiologic findings and clinical significance. *Korean J Radiol* 2001; 2: 138–144.
59. Yim APC. The role of video-assisted thoracoscopic surgery in the management of pulmonary tuberculosis. *Chest* 1996; 110: 829–832.
60. García-Yuste M, Ramos G, Duque JL, *et al.* Open-window thoracostomy and thoracomyoplasty to manage chronic pleural empyema. *Ann Thorac Surg* 1998; 65: 818–822.
61. Halezeroglu S, Keles M, Uysal A, *et al.* Factors affecting postoperative morbidity and mortality in destroyed lung. *Ann Thorac Surg* 1997; 64: 1635–1638.
62. Conlan AA, Lukanich JM, Shutz J, *et al.* Elective pneumonectomy for benign lung disease: modern-day mortality and morbidity. *J Thorac Cardiovasc Surg* 1995; 110: 1118–1124.
63. Odell JA, Henderson BJ. Pneumonectomy through empyema. *J Thorac Cardiovasc Surg* 1985; 89: 423.
64. Pomerantz M. Surgery for the management of *Mycobacterium tuberculosis* and nontuberculous mycobacterial infections of the lung. *In*: Shields TW, LeCicero J, Ponn RB, eds. General Thoracic Surgery. 5th Edn. Philadelphia, Lippincott Williams and Wilkins, 2000; pp. 1066–1075.
65. Swoboda L, Laule K, Blattmann H, *et al.* Improving function by decortication. Functional studies with particular evaluation of lung perfusion scintigraphy. *Helv Chir Acta* 1991; 57: 631–636.
66. Olgac G, Yilmaz MA, Ortakoylu MG, *et al.* Decision-making for lung resection in patients with empyema and collapsed lung due to tuberculosis. *J Thorac Cardiovasc Surg* 2005; 130: 131–135.
67. Shiraishi Y, Nakajima Y, Koyama A, *et al.* Morbidity and mortality after 94 extrapleural pneumonectomies for empyema. *Ann Thorac Surg* 2000; 70: 1202–1207.
68. Odell JA, Buckels NJ. Techniques of pneumonectomy. Pneumonectomy through an empyema. *Chest Surg Clin North Am* 1999; 9: 369–378.
69. Hopkins RA, Ungerleider RM, Staub EW, *et al.* The modern use of thoracoplasty. *Ann Thorac Surg* 1985; 40: 181–187.
70. Massard G, Olland A, Santelmo N, *et al.* Surgery for the sequellae of postprimary tuberculosis. *Thorac Surg Clin* 2012; 22: 287–300.
71. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, *et al.* Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007; 132: 1565–1572.
72. King PT, Holdsworth SR, Freezer NJ, *et al.* Outcome in adult bronchiectasis. *COPD* 2005; 2: 27–34.
73. Tsang KW, Tipoe GL. Bronchiectasis: not an orphan disease in the East. *Int J Tuberc Lung Dis* 2004; 8: 691–702.
74. Kato R, Kakizaki T, Hangai N, *et al.* Bronchoplastic procedures for tuberculous bronchial stenosis. *J Thorac Cardiovasc Surg* 1993; 106: 1118–1121.
75. Lee HS, Oh JY, Lee JH, *et al.* Response of pulmonary tuberculomas to antituberculous treatment. *Eur Respir J* 2004; 23: 452–455.
76. Doroshenkova AE, Grebennikov S, Kozhemyakin A, *et al.* Primary and repeated operations in surgery of TB. VII Congress of the Russian Phthisiatricians: Tuberculosis Today, 2003; Abstract P277.
77. Houben EN, Nguyen L, Pieters J. Interaction of pathogenic mycobacteria with the host immune system. *Curr Opin Microbiol* 2006; 9: 76–85.
78. Kaufmann SH. Protection against tuberculosis: cytokines, T cells, and macrophages. *Ann Rheum Dis* 2002; 61: Suppl. 2, ii54–ii58.
79. American Thoracic Society. Diagnostic standards and classification of tuberculosis. *Am Rev Respir Dis* 1990; 142: 725–735.
80. Levashev YN, Repin YM. Manual of Pulmonary and Extra-pulmonary Tuberculosis. St Petersburg, ELBI, 2008; p. 191.
81. Mathur PN, Wolf KM, Busk MF, *et al.* Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Chest* 1996; 110: 718–723.
82. Watanabe M, Hasegawa N, Ishizaka A, *et al.* Early pulmonary resection for *Mycobacterium avium* complex lung disease treated with macrolides and quinolones. *Ann Thorac Surg* 2006; 81: 2006–2030.
83. Abbasi-Dezfouli A, Daneshvar-Kakhki A, Farzanegan R, *et al.* Results of lobectomy and pneumonectomy in pulmonary TB. *Tanaffos* 2003; 2: 33–39.

84. Fujimoto T, Zaboura G, Fechner S, *et al.* Completion pneumonectomy: current indications, complications, and results. *J Thorac Cardovasc Surg* 2001; 121: 484–490.
85. Kiral H, Kosar A, Orki A, *et al.* Completion pneumonectomy: indications, complications, and results. *Tuberk Toraks* 2004; 52: 56–62.
86. Jarand JM, Levin A, Zhang L, *et al.* Clinical and microbiologic outcomes in patients receiving treatment for *Mycobacterium abscessus* pulmonary disease. *Am J Respir Crit Care Med* 2009; 179: A4053.
87. Hopkins RA, Ungerleider RM, Staub EW, *et al.* The modern use of thoracoplasty. *Ann Thorac Surg* 1985; 40: 181–187.
88. Kravchenko AF. The new method "cascade" thoracoplasty in surgery of destructive pulmonary tuberculosis. *Probl Tuberk Bolezn Legk* 2004; 3: 15–18.

Chapter 4

Fungal pulmonary infections: the conservative approach

Matteo Bassetti and Elda Righi

SUMMARY: Invasive fungal infections have increased worldwide and represent a threat for immunocompromised patients, including those who are HIV infected, recipients of solid organ and stem cell transplants, and patients receiving immunosuppressive therapies. High mortality rates and difficulties in early diagnosis characterise pulmonary fungal infections. In this chapter, invasive pulmonary aspergillosis, cryptococcosis and *Pneumocystis jirovecii* pneumonia have been reviewed, focusing on clinical aspects and therapeutic management. Although new compounds have become available in recent years (*e.g.* amphotericin B lipid formulations, third-generation azoles and echinocandins), new diagnostic tools and careful therapeutic management are mandatory to ensure an early appropriate targeted treatment, which is the key to a successful conservative approach in respiratory fungal infections.

Infectious Diseases Division, Santa Maria Misericordia University Hospital, Udine, Italy.

Correspondence: M. Bassetti, Infectious Diseases Division, Santa Maria Misericordia University Hospital, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy. Email: mattba@tin.it

Eur Respir Monogr 2013; 61: 37–49.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040412
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Pulmonary fungal infections are less common than bacterial and viral respiratory infections and often pose diagnostic difficulties. Over recent years, the incidence of fungal pulmonary infections has increased, due to the growing number of immunocompromised patients [1].

The lung represents the natural port of entry for most of these pathogens, which result in severe involvement in the clinical syndrome and association with high mortality rates [2]. Immunodeficiency, either owing to an underlying disease (*e.g.* HIV infection or haematological malignancies with neutropenia) or through the use of immunosuppressants (*e.g.* following organ transplantation or due to autoimmune inflammatory disorders), represents the principal risk factor for the most common respiratory invasive fungal infections, such as acute pulmonary aspergillosis, cryptococcosis and *Pneumocystis jirovecii* pneumonia (PJP) [3]. Nevertheless, the field of respiratory mycosis continues to evolve and develop, with many key advances recently occurring due to a significant growth in the number of diagnosed pulmonary fungal infections. Particularly, diagnostic methods and treatment options have expanded through the use of high-resolution imaging (computed tomography (CT) and positron emission tomography scans) and invasive diagnostic techniques (bronchoscopy, mediastinoscopy and video-assisted thoracoscopic biopsy, and CT-guided biopsy) that are recommended if invasive fungal infections are suspected [4, 5]. Furthermore, besides standard microbiological assays, noncultivation-dependent methods may add important elements to invasive fungal infection diagnosis in high-risk patients [6, 7].

As a consequence of the availability of several antifungal compounds such as echinocandins and extended-spectrum triazoles, new guidelines, recommendations, and the results of a number of multicentre randomised trials have been published. Despite these recent advances, efforts to develop early diagnostic tools (*e.g.* real-time PCR) and the optimisation of well-designed multicentre evaluations of diagnostic methods and therapeutic regimens available at present are still warranted. In this chapter, we have reviewed the main aspects for recognition, diagnosis and management for the three main aetiological agents of pulmonary mycoses that may pose significant risks especially for patients with impaired host defences. Less common invasive mycoses (*i.e.* mucormycosis, fusariosis, *etc.*) have not been included in this review.

Aspergillosis

Aspergillus spp. belong to the class of saprophytic fungi that grow on organic debris. Although hundreds of species have been recognised, only a few are implicated in human disease. In particular, 90% of cases of pulmonary disease are caused by *Aspergillus fumigatus*, due to its production of small spores that can penetrate inside the alveoli [8]. Amongst other species, *Aspergillus terreus* is responsible for less than 5% of invasive forms and *Aspergillus niger* and *Aspergillus flavus* can cause pulmonary and sinus disease.

Autopsy studies have shown the emergence of Aspergillus as a major pathogen due to an expansion of the spectrum of patients at risk for invasive aspergillosis. An observational study over a 12-year period in a patient population at an academic hospital evidenced an increase of invasive fungal infections from 2.2% to 5.1% that was mainly in association with a growth in the rate of Aspergillus infection [9]. Nevertheless, the real incidence of invasive aspergillosis is difficult to estimate due to the challenges in discriminating between *Aspergillus* colonisation and infection, a low number of autopsies performed that can prove definite diagnosis, and the absence of specific radiological signs especially in non-neutropenic patients.

Considering that *Aspergillus* virulence factors are of a multifactorial origin, the principal element linked to the disease presentation and progression remains the host immune status [10]. Specifically, the alveolar macrophages have a conidiocidal activity that may be impaired by steroid suppression [11]. Furthermore, the second line of defence from conidia that have germinated into hyphae is constituted by neutrophils that may be lacking or not functioning in case of chemotherapy or leukaemia [12]. Finally, T-cell dysregulation contributes to persistent and invasive *Aspergillus* infection [13].

Thus, *Aspergillus* species produce a spectrum of diseases that may present with features typically related to host factors [14]. Besides disseminated and invasive aspergillosis, other forms include allergic bronchopulmonary aspergillosis, aspergilloma, chronic necrotising aspergillosis, tracheobronchitis and acute invasive rhinosinusitis.

Aggressive forms of invasive aspergillosis typically occur in immunocompromised patients. Conversely, chronic forms of pulmonary aspergillosis, such as chronic necrotising pulmonary aspergillosis or fibrocavitary aspergillosis, which progress over months to years, are more often seen in patients without severe immune deficiency and may complicate existing lung diseases associated with cavities or bullae.

Acute invasive pulmonary aspergillosis

Aggressive forms of acute invasive aspergillosis typically occur in patients with impaired immune systems, such as haematological patients, recipients of solid organ transplants and, less commonly, patients with advanced HIV infection [15]. Typical features include the presence of hyphal angioinvasion with vascular thrombosis and tissue infarction. Normally, scant inflammatory response is present due to the lack of immune activation. Possible evolution is represented by lung cavitation. The main risk factor for this acute clinical presentation is represented by neutropenia

(*i.e.* acute leukaemia, stem cell transplant and chemotherapy). The clinical signs and symptoms are often nonspecific. Fever is commonly present and may be associated with dry cough, chest pain and occasionally haemoptysis [16].

Recipients of solid organ transplants, characterised mainly by T-cell impairment in the first 6 months after the transplant, often present with acute inflammatory pneumonia. In particular, chronic necrotising aspergillosis and tracheobronchitis affecting the anastomotic site can progress, causing dehiscence in lung transplant recipients [17].

In HIV-infected patients who have progressed to AIDS, acute to slowly progressive necrotising pneumonia due to *Aspergillus* infection may present variable histological findings with neutrophilic infiltrates, vascular invasion, pulmonary abscesses and cavitation.

Chronic pulmonary aspergillosis

Other chronic forms of Aspergillus infection of the lung have been described, namely chronic necrotising pulmonary aspergillosis, symptomatic pulmonary aspergilloma and Aspergillus pseudotuberculosis. The distinction between subacute invasive pulmonary aspergillosis, chronic necrotising pulmonary aspergillosis and aspergilloma has not been well defined, and an overlap in clinical and radiological features among these different forms exists. Subacute invasive pulmonary aspergillosis has been associated with advanced HIV infection, chronic granulomatous disease, diabetes mellitus, alcoholism and corticosteroid therapy [18]. Subacute and chronic forms of pulmonary aspergillosis (*e.g.* chronic necrotising pulmonary aspergillosis or fibrocavitary aspergillosis) typically occur in patients without severe immune impairment where the inflammatory response plays a role into disease progression. Developing pneumonia is generally characterised by pyogranulomatous inflammation without hyphal vascular invasion or coagulative necrosis. Weight loss, chronic cough (often with haemoptysis and shortness of breath), fatigue and chest pain represent the most common symptoms.

A study has recognised three distinct radiological patterns of non-acute infection: chronic cavitary pulmonary aspergillosis, characterised by the formation and expansion of multiple cavities possibly containing fungus balls; chronic fibrosing pulmonary aspergillosis, with an extensive pulmonary fibrosis; and subacute invasive pulmonary aspergillosis, with enlargement of a single cavity, usually with a thin wall, occurring slowly over months or rapidly in weeks [19]. Since risk factors such as diabetes and corticosteroid use are commonly associated with these forms, it is estimated that chronic pulmonary aspergillosis has a high global disease burden and is associated with significant under diagnosis. Furthermore, other risk groups for invasive aspergillosis include patients with chronic obstructive pulmonary disease and patients with cirrhosis due to a generalised depressed phagocytosis status. The analysis of a group of 16 patients with chronic obstructive pulmonary disease receiving steroid treatment, who had proven or probable invasive aspergillosis, required intensive care unit admission and displayed poor outcomes [20]. Furthermore, with the introduction of new monoclonal immunosuppressive agents it is expected that new categories at risk for invasive aspergillosis will arise [21].

Diagnosis of aspergillosis

Definitive diagnosis of aspergillosis requires mould isolation from a culture and the histological documentation of the hyphae from tissue samples [22]. Given the infiltrative nature of *Aspergillus*, a low spread in the bronchial tree normally occurs, thus contributing to a low sensitivity (around 40%) of respiratory tract culture specimens, including sputum samples and bronchoalveolar lavage (BAL) [8, 23]. Nevertheless, isolation of *Aspergillus* from cultures has been associated with a high predictive value for subsequent invasive disease in immunodeficient patients [24].

Given the difficulties in laboratory isolation of *Aspergillus*, growing attention has been focused on noncultivation-dependent methods such as detection of antigens and PCR. Specific mould antigens from blood and BAL samples have now been accepted as an important tool for *Aspergillus*

diagnosis [25]. In particular, the galactomannan (GM) enzyme-linked immunosorbent assay (Platelia Aspergillus ELISA; Bio-Rad Laboratories, Redmond, Washington, DC, USA) detects a component of cell walls secreted from growing hyphae and has been approved by the US Food and Drug Administration (FDA) for invasive aspergillosis diagnosis [26]. Variable sensitivity (from 29% to 100%) and high specificity (from 81% to 98%) have been reported when the recommended serial testing of at least twice a week is performed [27]. Early GM positivity has been shown up to 8 days before culture positivity and the onset of symptoms in 65% and 40% of haematopoietic stem cell transplant (HSCT) recipients, respectively [28].

Controversies are reported for the use of different cut-off values for GM index (defined as ELISA optical density ratio between the sample and standard threshold of 1 $ng \cdot mL^{-1}$). In HSCT recipients, lower thresholds (*i.e.* a single GM index $\geqslant 0.7$ or a dynamic cut-off of two consecutive GM values >0.5) allowed for better sensitivities and earlier detection of disease [29]. GM detection from other fluids in haematological patients showed promising results. The GM optical index from BAL samples showed higher specificity and sensitivity and a better correlation with the European Organisation for Research and Treatment of Cancer (EORTC) classification of proven and probable invasive aspergillosis, compared with serum GM detection [30].

One study performed in HSCT recipients showed that an increase in GM during the first week of therapy was predictive of treatment failure [31]. Thus, having the potential for treatment monitoring and prognostic application, GM detection has been proposed as a surrogate end-point for outcome [32].

GM false positives may occur due to gastrointestinal translocation or the presence of GM in antibiotics or enteral nutrition solutions (*e.g.* amoxicillin-clavulanate and piperacillin/tazobactam use is correlated with up to 70% false-positive GM tests) [33–35], while decreased sensitivity may be present if patients have already received mould-active drugs such as caspofungin [36, 37].

Other techniques for invasive aspergillosis diagnosis include 1,3-β-D-glucan testing, which has nowadays found wide application in the diagnosis of invasive candidiasis and PJP, and real-time PCR, which is currently being studied. Since it has been demonstrated to appear normal in up to 30% of patients in the week preceding the exitus due to invasive aspergillosis, chest radiography is an unreliable tool for diagnosis of invasive aspergillosis. A CT scan represents the imaging of choice for the detection of pulmonary aspergillosis and should also be considered in high-risk patients [38].

Generally, radiographic presentation varies from a single nodular lesion that merges into larger masses to diffuse bilateral pulmonary infiltrates. Two classic radiological findings that are considered typically associated to aspergillosis are the "halo" sign, a rim of ground-glass opacity that surrounds a nodule in neutropenic patients during the early stage of invasive aspergillosis, and the "air crescent" sign, a cavitated lesion with an intracavitary mass and a surrounding rim of air appearing in around 50% of patients approximately one week after recovery of neutrophil function and number [39]. Although suggestive indicators, these signs are nonspecific and can be found in other fungal and bacterial infections and even in non-infectious lesions such as pulmonary haemorrhage [40].

Treatment of aspergillosis

In recent years, important advances have been made in the management of *Aspergillus* spp. infection, and new antifungal drugs have become available for the treatment of invasive forms of aspergillosis. The treatment options for invasive pulmonary aspergillosis are summarised in table 1.

Amphotericin B (AMB) has represented the gold standard for the management of invasive aspergillosis until azole compounds became available. Lipid formulations of AMB (*e.g.* liposomal (L)-AMB and lipid complex AMB) greatly improved the toxicity profile of polyenes, although they did not show increased efficacy compared with conventional AMB deoxycholate (dAMB). Although immunocompromised patients often have difficulties in tolerating dAMB nephrotoxicity and have

Table 1. Primary and alternative treatments for pulmonary invasive aspergillosis

Primary targeted treatment	Alternative	Salvage
Recommended		
Voriconazole orally or *i.v.*, loading dose 6 mg·kg^{-1} every 12 h on day 1, then 4 mg·kg^{-1} every 12 h; oral formulation if creatine clearance <50 mL·min^{-1} (200 mg every 12 h)	Liposomal amphotericin B *i.v.*, 3–5 mg·kg^{-1}·day^{-1}, or lipid complex amphotericin B *i.v.*, 5 mg·kg^{-1}·day^{-1}	Caspofungin *i.v.*, 70 mg on day 1, then 50 mg·day^{-1}, or micafungin *i.v.*, 100–150 mg·day^{-1}
	Not routinely recommended	
	Combination therapy (the association of an echinocandin with voriconazole may be considered in individual patients)	Posaconazole orally, 200 mg every 6 h until stabilisation, then 400 mg every 12 h

infusion-related adverse effects, no large randomised studies have been performed to date to compare the efficacy of different AMB formulations [41, 42]. A comparative study evaluating low *versus* high doses (3 *versus* 10 mg·kg^{-1}·day^{-1}) of L-AMB demonstrated that higher doses did not lead to better outcomes compared with lower doses, but the utility of high doses was not compared with other compounds that are active towards invasive aspergillosis [43].

Antifungal management has changed with the introduction of a third-generation azole, voriconazole, which was approved by the US FDA in 2002 for the primary treatment of aspergillosis, and has shown efficacy in clinical response and increased survival rates in a large randomised trial [44]. Furthermore, a class of echinocandins has demonstrated efficacy in aspergillosis therapy and caspofungin was approved for the treatment of refractory invasive aspergillosis in 2001 [45].

Posaconazole was also approved as a prophylactic agent in high-risk patients to prevent invasive aspergillosis, and studies that used it as a salvage therapy showed favourable outcomes suggesting a possible role in primary therapy [46, 47].

The duration of therapy for most conditions of aspergillosis has not been optimally defined and it is often based on clinical resolution of symptoms and protracted throughout the duration of the critical period of immunosuppression [22]. Because chronic necrotising pulmonary aspergillosis requires an extended course of therapy lasting for months, an orally administered triazole, such as voriconazole, is preferred over a parenterally administered agent [48, 49]. In the group of solid organ transplant recipients, although representing the drug of choice, voriconazole use warrants frequent assessment of plasmatic levels through follow-up by therapeutic drug monitoring, in order to avoid drug-related toxicity due to the known pharmacological interference of the azole class with immunosuppressants [50].

As a consequence of a larger antifungal armamentarium, more combinations can now be tested for potentially synergic effects in invasive aspergillosis treatment. Promising results were shown by the combination of voriconazole and amphotericin products with echinocandins [51, 52]. Nevertheless, no definite clinical evidence for the efficacy of combination therapy has so far been available. The results of a multicentre, randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin *versus* voriconazole monotherapy for primary treatment of invasive aspergillosis in haematological patients are currently under evaluation. Combination therapy was administered to 454 patients for 2–4 weeks during a minimum of 6 weeks of treatment. Preliminary results indicated that, although a global response was apparently higher in monotherapy *versus* combination therapy recipients, results of subgroup analyses showed that association of voriconazole and anidulafungin significantly increased the rate of overall 6-week survival in the subset of patients with antigen-diagnosed disease [53].

Large surveillance reports have found evidence that respiratory azole resistance to *A. fumigatus* is increasing across Europe, with rates of around 6% [54]. These data need to be confirmed worldwide and may have implications in the future treatment of the disease.

PJP

Pneumocystis jirovecii, previously known as *Pneumocystis carinii*, was initially classified as a protozoan and subsequently as a fungus on the basis of genetic and biochemical analyses. The main morphological states identified microscopically are a unicellular trophic form, the trophozoite, and a mature form, the cyst, which is considered the diagnostic structure of the *Pneumocystis* [55]. *P. jirovecii* is ubiquitous and seroconversion occurs in up to 85% of children up to age 2 years [56]. Primary infection is always asymptomatic with no apparent colonisation; re-activation of the disease or re-infection with different organism genotypes can occur in previously infected patients during periods of severe immunosuppression [57, 58].

Host defences against *Pneumocystis* include alveolar macrophages, B-cells, and CD4+ T-cells. Specifically, HIV-infected patients, patients with haematological malignancies, recipients of solid organ transplantation, and those receiving immune-suppressive drugs (*e.g.* corticosteroids or tumour necrosis factor (TNF)-α antagonists) for inflammatory disorders are all at risk for PJP [59].

Although disseminated infections are reported, *Pneumocystis* has a predilection for the lungs and it is known to cause life-threatening pneumonia (PJP) in immunocompromised patients [60]. The trophozoite attaches to the alveolar type I pneumocytes, causing massive inflammation and interstitial oedema [59]. Symptoms include fever, cough, shortness of breath and hypoxaemia; delayed diagnosis and late treatment may cause respiratory failure and death.

In a study encompassing 451 HIV-infected patients diagnosed with PJP, risk factors for mortality included age, recent use of injected drugs, elevated bilirubin levels, low serum albumin, and an alveolar–arterial oxygen gradient below 50 mmHg. Using these factors, the risk of mortality ranged from 4% if none or one risk factor were present to 48% in the presence of four or five predictors [61].

Although the most common radiographical findings are interstitial pulmonary infiltrates, PJP may present with diffuse bilateral alveolar infiltrates, cavitated nodules and granulomas [62]. The mainstay for the diagnosis of PJP is microscopic examination of the BAL, with identification of cysts with methenamine silver stain. The possibility of diagnosing PJP on BAL is quite high in patients immunosuppressed by HIV infection, reaching 90% and 70% by microscopical examination in BAL and sputum, respectively [63]. Conversely, patients with PJP without HIV infection have much lower diagnostic yield with standard microscopy compared with HIV-infected patients, displaying negligible rates in repeated induced sputum and positivity for *P. jirovecii* in BAL samples below 20% [63–65]. An alternative method for the diagnosis of PJP is represented by the serum assay for 1,3-β-D-glucan [66].

The drug of choice for severe PJP remains trimethoprim (TMP)-sulfamethoxazole (SMX) [67]. Since the cell wall of *P. jirovecii* does not contain ergosterol, the target of azoles and polyenes, but 1,3-β-D-glucan, the echinocandins have been demonstrated to be the only effective antifungals for PJP [68, 69]. Although the use as a salvage treatment in PJP showed promising results, controlled clinical trials with echinocandins are still lacking [70]. As reported in table 2, the association of primaquine and clindamycin or the intravenous administration of pentamidine may be used as alternatives.

The use of corticosteroids has demonstrated a significant benefit to HIV-infected patients with moderate to severe PJP in a comparative study of 333 patients receiving adjunctive prednisone compared with patients not receiving corticosteroids. Reduced respiratory failure and 3-month death rates were demonstrated in the group of patients treated with corticosteroid and showing hypoxaemia (defined by arterial oxygen tension on room air of $<$70 mmHg) compared with the standard

Table 2. Therapeutic and prophylactic options for *Pneumocystis jirovecii* pneumonia

Regimen	Therapeutic	Prophylactic[#]
Preferred	TMP-SMX (TMP 15–20 mg·kg^{-1}·day^{-1} and SMX 75–100 mg·kg^{-1}·day^{-1}) in four daily doses, plus prednisone (or equivalent dose of other corticosteroid started before TMP-SMX) if P_{aO_2} <70 mmHg for 21 days, 40 mg twice daily for 5 days, then 40 mg daily for 5 days, then 20 mg daily for 11 days; therapy generally continued for 3 weeks	TMP-SMX one double-strength tablet (160 mg as TMP) orally three times weekly, or TMP-SMX one single-strength tablet (80 mg as TMP) orally daily; generally continued for 6 months post transplant or until CD4 cell recovery in HIV-infected patients
Alternative	Primaquine 30 mg·day^{-1} and clindamycin 600 mg three times daily, continued for 3 weeks, or pentamidine *i.v.* 4 mg·kg^{-1}·day^{-1}	Dapsone 100 mg orally daily, or atovaquone 1500 mg orally in two daily doses, or aerosolised pentamidine 300 mg once per month, or dapsone 50 mg orally daily plus pyrimethamine 50 mg weekly, or other combination therapies such as clindamycin plus primaquine or sulfadiazine plus pyrimethamine
Not recommended	Pentamidine aerosol in transplanted patients	Pentamidine aerosol in transplanted patients
No data	Echinocandins	Echinocandins

TMP: trimethoprim; SMX: sulfamethoxazole; P_{aO_2}: arterial oxygen tension. [#]: prophylaxis is recommended in patients at high risk for *Pneumocystis jirovecii* pneumonia (HIV-infected patients with CD4 count below 200 cells·mm^{-3}, transplant recipients, patients receiving highly immunosuppressive chemotherapy (*e.g.* purine analogues) and/or prolonged high dose steroids (>20 mg·day^{-1} for more than 4 weeks)).

treatment group [71]. Retrospective studies have also confirmed the benefit of corticosteroid use in addition to antibiotics in patients with severe PJP but not infected with HIV [72].

Prior to the use of routine antimicrobial prophylaxis, the incidence of PJP after stem cell transplant was reported to be as high as 15% [73]. Prophylaxis of immunosuppressed patients has greatly decreased the burden of *P. jirovecii* infection, making prevention the cornerstone of PJP treatment. Primary prophylaxis against PJP in HIV-infected adults should be given when the CD4 absolute cell count number falls below 200 cells·mm^{-3}, or as a lifelong secondary prophylaxis, until immune system reconstitution [74]. In fact, in a case analysis of 325 HIV-infected patients discontinuing prophylaxis with CD4 cell count greater than 200 cells·mm^{-3}, no cases of recurrent *Pneumocystis* infection were found during a prolonged follow-up period [75]. Recipients of solid organ or stem cell transplants should also receive prophylaxis [59].

HIV-negative patients receiving immunosuppressive medications should be evaluated on a case-by-case basis to recognise the effective risk of developing PJP [76]. In particular, the use of highly immunosuppressive chemotherapy (*i.e.* purine analogues) and/or the use of high-dose corticosteroids (*i.e.* greater than 20 mg of prednisone for a period of over 4 weeks), along with steroid dose tapering, represent recognised risk factors for PJP and prophylaxis is advised [76–78]. Nevertheless, although the use of anti-CD52 and anti-CD20 monoclonal antibodies, calcineurin inhibitors and TNF antagonists have been associated with an increased risk of *Pneumocystis* infection, a general recommendation for universal prophylaxis in patients receiving biologicals alone cannot be made until further studies are completed [79, 80].

Since the strategy of monitoring CD4 cell counts may fail to identify HIV-negative patients at risk for developing PJP [81], other factors such as overall immune dysregulation and careful evaluation of the immunosuppressive regimen should be taken into consideration [59].

TMP-SMX represents the mainstay for *Pneumocystis* prophylaxis. Common dosing regimens include one double-strength tablet (160 mg as TMP) three times per week or one single-strength

tablet (80 mg as TMP) daily [82]. Although the association of folate/folinate with TMP-SMX has been suggested in order to reduce the risk of marrow suppression, the topic remains controversial. Worse outcomes have been reported in a cohort of 92 AIDS patients treated with TMP-SMX plus folinic acid compared with TMP-SMX; nevertheless, the reasons remain unclear [83–85].

Alternative prophylaxis regimens in patients who cannot tolerate TMP-SMX due to marrow suppression or allergic dermatitis include dapsone (as a single agent or in combination with pyrimethamine), atovaquone, aerosolised pentamidine, and clindamycin plus primaquine [86–88]. Although used, aerosolised pentamidine may cause exposure to extrapulmonary infections and has been linked with worse outcomes in transplanted recipients, while dapsone and atovaquone need to be associated with pyrimethamine to obtain adequate prophylaxis against toxoplasmosis [89, 90].

Table 2 summarises the therapeutic and prophylactic options for PJP. In most severe cases, the recommendation is close observation in an intensive care setting. Since *P. jirovecii* demonstrates airborne transmission between infected and non-infected patients, adequate isolation measures should be taken for patients at risk for PJP.

Cryptococcosis

Cryptococcosis is due to infection with the encapsulated fungus *Cryptococcus neoformans*, an organism with a worldwide distribution. Inhalation of organisms represents the usual route of the infection, which may remain isolated in the lungs or undergo haematogenous spread and involve the central nervous system (CNS), bones and skin, depending on the host immune status [91]. The lungs are considered the initial site of almost all cryptococcal infections and the second most clinically relevant after the CNS. The pattern of pulmonary disease is extremely variable, ranging from asymptomatic airway colonisation to acute respiratory distress syndrome; the latter is mainly observed in immunocompromised patients [92]. Host alveolar macrophages, natural killer cells and CD4 T-cells are the most important defence mechanisms against *Cryptococcus*. Impaired T-cell-mediated immunity (AIDS, liver cirrhosis, renal failure, sarcoidosis, chronic lung disease, diabetes, HSCT and solid organ transplant) and treatment with long-term corticosteroids and TNF antagonists expose patients to a high risk of severe cryptococcal infection [93]. It is estimated that HIV-associated cryptococcosis reaches about one million cases annually worldwide [94–98].

Besides *C. neoformans*, another species is represented by *Cryptococcus gattii*, traditionally considered to be restricted geographically to tropical and subtropical climates but responsible for outbreaks in immunocompetent hosts in Canada and the northwest USA [99].

Mortality for cryptococcosis remains high, reaching 20% for acute meningoencephalitis in HIV patients [100] and being always fatal in the absence of a specific therapy [101]. Mortality in solid organ transplant recipients varied from 10% in patients with stable limited pulmonary disease to over 50% in those with acute respiratory failure requiring mechanical ventilation [102].

From a radiological point of view, features of pulmonary cryptococcosis may vary widely. The most frequent radiographical findings are peripheral nodules with lobar infiltrates, while mediastinal lymphadenopathy and pleural effusions occur less often [103]. Since cavitated or multiple nodular lung lesions are common findings, misdiagnosis may include lung cancer and pneumonia. In a review of 15 HIV-negative patients with proven pulmonary cryptococcosis, 70% were symptomatic [104]. The presentation features in HIV-negative immunocompromised patients with pulmonary cryptococcosis have been recently reviewed in 109 patients [105]. The most common symptoms were cough (61%), dyspnoea (48%), fever (29%), weight loss (19%), pleuritic chest pain (19%) and night sweats (16%).

It has been demonstrated that *Cryptococcus* spp. can be recovered from the sputum of asymptomatic individuals [106]. Nevertheless, in high-risk patients such as solid organ transplant recipients, identification of *Cryptococcus* in respiratory tract specimens warrants further

Table 3. Recommended regimens for cryptococcosis treatment in immunosuppressed and non-immunosuppressed patients

Disease state	Regimen
Immunosuppressed	
Mild-to-moderate disease (localised pulmonary infiltrates, mild immunosuppression, no dissemination)	Fluconazole *i.v.*/orally, 6–12 mg·kg^{-1} until stabilisation (4 months), then 200 mg daily for 6–12 months
Severe dissemination, CNS and pneumonia or ARDS	Liposomal amphotericin B *i.v.*, 3–4 mg·kg^{-1} per day, or lipid complex amphotericin B *i.v.*, 5 mg·kg^{-1} per day, plus flucytosine orally, 100 mg·kg^{-1} per day in four divided doses for at least 6 weeks, then fluconazole orally, 400–800 mg·day^{-1} for 6–18 months; corticosteroids if ARDS
Non-immunosuppressed	
Mild-to-moderate disease	Fluconazole orally, 6–12 mg·kg^{-1} until stabilisation (4 months), then 200 mg daily for 6–12 months, or voriconazole orally, 200 mg every 12 h, or posaconazole orally, 400 mg every 12 h
Severe dissemination or ARDS	As in immunosuppressed patients; corticosteroids if ARDS and inflammatory response

CNS: central nervous system; ARDS: acute respiratory distress syndrome.

investigation for invasive pulmonary disease. Furthermore, a positive serum cryptococcal antigen titre can be documented in around 80% of those with any pulmonary involvement and up to 95% and 97% of patients with CNS disease or disseminated cryptococcosis, respectively [107]. Thus, although a negative cryptococcal antigen result does not exclude the diagnosis of disseminated cryptococcosis, a positive serum cryptococcal antigen test in a transplant recipient warrants investigation for disseminated disease such as meningoencephalitis.

An update on clinical practice guidelines for the management of cryptococcal disease in HIV-positive, transplanted, and non-HIV non-transplanted patients was published by the Infectious Diseases Society of America in 2010 [108]. Overall, different therapeutic strategies apply to non-meningeal, pulmonary cryptococcosis in immunosuppressed and non-immunosuppressed patients. Specifically, immunosuppressed patients with pulmonary cryptococcosis should always undergo lumbar puncture to exclude meningitis. Table 3 includes the antifungal regimens used for cryptococcosis in immunosuppressed and non-immunosuppressed patients.

Conversely, a lumbar puncture can be avoided in immunocompetent hosts with asymptomatic pulmonary nodule or infiltrate, no CNS symptoms, and negative or very low serum cryptococcal antigen. While in HIV-infected patients, a cryptococcal antigen titre that is stably below 1:512 can be used to discontinue maintenance fluconazole, in non-immunosuppressed persistently positive serum, cryptococcal antigen titres are not a criterion for continuance of therapy.

Although limited in numbers, few studies have shown no difference in outcome when fluconazole was used instead of polyenes to treat stable respiratory cryptococcosis limited to the lungs [96]. In severe disease, polyenes represent the drug of choice, while fluconazole is used for maintenance therapy to be continued orally for several months.

Conclusions

Invasive fungal infections have increased worldwide due to a growing number of patients with advanced immune system dysregulation. Mortality remains high in this cohort and is enhanced by the organism virulence and an impaired immune response.

Although a surgical approach may be necessary in case of poor control of the infective source, the conservative approach has nowadays shown noticeable results thanks to the introduction of new

compounds into the antifungal armamentarium. Particularly, less toxic AMB formulations, third-generation azoles and echinocandins play a crucial role in invasive fungal infection management. Nevertheless, appropriate treatment duration, combination therapy and therapeutic drug monitoring should be carefully considered on a case-by-case basis to avoid the emergence of antifungal resistance that would undermine the successful outcome of life-threatening infections. Despite the new advances in invasive fungal infection diagnosis that have been made, standardisation of real-time PCR testing, routine detection of GM in BAL, and extensive 1,3-β-D-glucan use are awaited. These would favour early diagnosis and a prompt targeted treatment of invasive respiratory fungal infections.

Statement of Interest

M. Bassetti has been a Board member for Pfizer, MSD, Astellas and Gilead, has received grants from Pfizer and MSD, and has received payment for lectures from Pfizer, MSD and Astellas.

References

1. Kauffman CA. Fungal infections. *Proc Am Thorac Soc* 2006; 3: 35–40.
2. Tunnicliffe G, Schomberg L, Walsh S, *et al.* Airway and parenchymal manifestations of pulmonary aspergillosis. *Respir Med* 2013 [In press DOI: 10.1016/j.rmed.2013.03.016].
3. Person AK, Kontoyiannis DP, Alexander BD. Fungal infections in transplant and oncology patients. *Hematol Oncol Clin North Am* 2011; 25: 193–213.
4. Nosari A, Anghilieri M, Carrafiello G, *et al.* Utility of percutaneous lung biopsy for diagnosing filamentous fungal infections in hematologic malignancies. *Haematologica* 2003; 88: 1405–1409.
5. Marom EM, Kontoyiannis DP. Imaging studies for diagnosing invasive fungal pneumonia in immunocompromised patients. *Curr Opin Infect Dis* 2011; 24: 309–314.
6. Wood BR, Komarow L, Zolopa AR, *et al.* Test performance of blood β-glucan for *Pneumocystis jirovecii* pneumonia in patients with AIDS and respiratory symptoms. *AIDS* 2013; 27: 967–972.
7. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. *Clin Infect Dis* 2006; 42: 1417–1427.
8. Perfect JR, Cox GM, Lee JY, *et al.* The impact of culture isolation of *Aspergillus* species: a hospital-based survey of aspergillosis. *Clin Infect Dis* 2001; 33: 1824–1833.
9. Groll AH, Shah PM, Mentzel C, *et al.* Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect* 1996; 33: 23–32.
10. Latge JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev* 1999; 12: 310–350.
11. Schaffner A. Macrophage–*Aspergillus* interactions. *Immunol Ser* 1994; 60: 545–552.
12. Scheneemann M, Schaffner A. Host defense mechanism in *Aspergillus fumigatus* infections. *In*: Brakhage AA, Jahn B, Schmidt A, eds. *Aspergillus fumigatus*: Biology, Clinical Aspects, and Molecular Approaches to Pathogenicity. Vol. 2. Basel, Karger, 1999; pp. 57–68.
13. Cenci E, Mencacci A, Fe d'Ostiani C, *et al.* Cytokine- and T helper-dependent lung mucosal immunity in mice with invasive pulmonary aspergillosis. *J Infect Dis* 1998; 178: 1750–1760.
14. Segal BH. Aspergillosis. *N Engl J Med* 2009; 360: 1870–1884.
15. Stergiopoulou T, Meletiadis J, Roilides E, *et al.* Host-dependent patterns of tissue injury in invasive pulmonary aspergillosis. *Am J Clin Pathol* 2007; 127: 349–355.
16. Meyers JD. Fungal infections in bone marrow transplant patients. *Semin Oncol* 1990; 17: 10–13.
17. Iversen M, Burton CM, Vand S, *et al. Aspergillus* infection in lung transplant patients: incidence and prognosis. *Eur J Clin Microbiol Infect Dis* 2007; 26: 879–886.
18. Denning DW. Chronic forms of pulmonary aspergillosis. *Clin Microbiol Infect* 2001; 7: Suppl. 2, 25–31.
19. Denning DW, Riniotis K, Dobrashian R, *et al.* Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003; 37: Suppl. 3, S265–S280.
20. Bulpa PA, Dive AM, Garrino MG, *et al.* Chronic obstructive pulmonary disease patients with invasive pulmonary aspergillosis: benefits of intensive care? *Intensive Care Med* 2001; 27: 59–67.
21. Martin SI, Marty FM, Fiumara K, *et al.* Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. *Clin Infect Dis* 2006; 43: 16–24.
22. Walsh TJ, Anaissie EJ, Denning DW, *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46: 327–360.
23. Levy H, Horak DA, Tegtmeier BR, *et al.* The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. *Respir Med* 1992; 86: 243–248.
24. Wald A, Leisenring W, van Burik JA, *et al.* Epidemiology of *Aspergillus* infections in a large cohort of patients undergoing bone marrow transplantation. *J Infect Dis* 1997; 175: 1459–1466.

25. Ascioglu S, Rex JH, de Pauw B, *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; 34: 7–14.
26. Latge JP. Antigen and DNA patterns characteristic of *Aspergillus fumigatus*. *Contrib Microbiol* 1999; 2: 69–87.
27. Denning DW, Evans EG, Kibbler CC, *et al.* Guidelines for the investigation of invasive fungal infections in haematological malignancy and solid organ transplantation. British Society for Medical Mycology. *Eur J Clin Microbiol Infect Dis* 1997; 16: 424–436.
28. Sulahian A, Boutboul F, Ribaud P, *et al.* Value of antigen detection using an enzyme immunoassay in the diagnosis and prediction of invasive aspergillosis in two adult and pediatric hematology units during a 4-year prospective study. *Cancer* 2001; 91: 311–318.
29. Maertens JA, Klont R, Masson C, *et al.* Optimization of the cutoff value for the *Aspergillus* double-sandwich enzyme immunoassay. *Clin Infect Dis* 2007; 44: 1329–1336.
30. Meersseman W, Lagrou K, Maertens J, *et al.* Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med* 2008; 177: 27–34.
31. Miceli MH, Grazziutti ML, Woods G, *et al.* Strong correlation between serum *Aspergillus* galactomannan index and outcome of aspergillosis in patients with hematological cancer: clinical and research implications. *Clin Infect Dis* 2008; 46: 1412–1422.
32. Maertens J, Buve K, Theunissen K, *et al.* Galactomannan serves as a surrogate endpoint for outcome of pulmonary invasive aspergillosis in neutropenic hematology patients. *Cancer* 2009; 115: 355–362.
33. Viscoli C, Machetti M, Cappellano P, *et al.* False-positive galactomannan platelia *Aspergillus* test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004; 38: 913–916.
34. Girmenia C, Santilli S, Ballaro D, *et al.* Enteral nutrition may cause false-positive results of *Aspergillus* galactomannan assay in absence of gastrointestinal diseases. *Mycoses* 2011; 54: e883–e884.
35. Mattei D, Rapezzi D, Mordini N, *et al.* False-positive *Aspergillus* galactomannan enzyme-linked immunosorbent assay results *in vivo* during amoxicillin-clavulanic acid treatment. *J Clin Microbiol* 2004; 42: 5362–5363.
36. Maertens J, Verhaegen J, Lagrou K, *et al.* Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. *Blood* 2001; 97: 1604–1610.
37. Marr KA, Laverdiere M, Gugel A, *et al.* Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. *Clin Infect Dis* 2005; 40: 1762–1769.
38. Rhame FS, Streifel AJ, Kersey JH Jr, *et al.* Extrinsic risk factors for pneumonia in the patient at high risk of infection. *Am J Med* 1984; 76: 42–52.
39. Saugier-Veber P, Devergie A, Sulahian A, *et al.* Epidemiology and diagnosis of invasive pulmonary aspergillosis in bone marrow transplant patients: results of a 5 year retrospective study. *Bone Marrow Transplant* 1993; 12: 121–124.
40. Won HJ, Lee KS, Cheon JE, *et al.* Invasive pulmonary aspergillosis: prediction at thin-section CT in patients with neutropenia – a prospective study. *Radiology* 1998; 208: 777–782.
41. Walsh TJ, Hiemenz JW, Seibel NL, *et al.* Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis* 1998; 26: 1383–1396.
42. Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. *Clin Infect Dis* 1998; 27: 603–618.
43. Cornely OA, Maertens J, Bresnik M, *et al.* Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis* 2007; 44: 1289–1297.
44. Herbrecht R, Denning DW, Patterson TF, *et al.* Voriconazole *versus* amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.
45. Kartsonis NA, Saah AJ, Lipka CJ, *et al.* Salvage therapy with caspofungin for invasive aspergillosis: results from the caspofungin compassionate use study. *J Infect* 2005; 50: 196–205.
46. Cornely OA, Maertens J, Winston DJ, *et al.* Posaconazole *vs.* fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; 356: 348–359.
47. Walsh TJ, Raad I, Patterson TF, *et al.* Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. *Clin Infect Dis* 2007; 44: 2–12.
48. Camuset J, Nunes H, Dombret MC, *et al.* Treatment of chronic pulmonary aspergillosis by voriconazole in nonimmunocompromised patients. *Chest* 2007; 131: 1435–1441.
49. Sambatakou H, Dupont B, Lode H, *et al.* Voriconazole treatment for subacute invasive and chronic pulmonary aspergillosis. *Am J Med* 2006; 119: 527.e17–e24.
50. Johnson HJ, Han K, Capitano B, *et al.* Voriconazole pharmacokinetics in liver transplant recipients. *Antimicrob Agents Chemother* 2010; 54: 852–859.
51. Perea S, Gonzalez G, Fothergill AW, *et al. In vitro* interaction of caspofungin acetate with voriconazole against clinical isolates of *Aspergillus* spp. *Antimicrob Agents Chemother* 2002; 46: 3039–3041.
52. Kirkpatrick WR, Perea S, Coco BJ, *et al.* Efficacy of caspofungin alone and in combination with voriconazole in a guinea pig model of invasive aspergillosis. *Antimicrob Agents Chemother* 2002; 46: 2564–2568.

53. Marr KA, Schlamm H, Rottinghaus ST, *et al.* A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin *versus* voriconazole monotherapy for primary treatment of invasive aspergillosis. London, 22nd European Congress of Clinical Microbiology and Infectious Diseases, 2012; Poster LB2812.
54. Snelders E, van der Lee HA, Kuijpers J, *et al.* Emergence of azole resistance in *Aspergillus fumigatus* and spread of a single resistance mechanism. *PLoS Med* 2008; 5: e219.
55. Orenstein A, Masur H. A diagnostic approach to *Pneumocystis jiroveci* pneumonia. *In*: Maertens JA, Marr KA, eds. Diagnosis of Fungal Infections. New York, Informa Healthcare, 2007; pp. 267–290.
56. Pifer LL, Hughes WT, Stagno S, *et al. Pneumocystis carinii* infection: evidence for high prevalence in normal and immunosuppressed children. *Pediatrics* 1978; 61: 35–41.
57. Nevez G, Magois E, Duwat H, *et al.* Apparent absence of *Pneumocystis jirovecii* in healthy subjects. *Clin Infect Dis* 2006; 42: e99–e101.
58. Kovacs JA, Gill VJ, Meshnick S, *et al.* New insights into transmission, diagnosis, and drug treatment of *Pneumocystis carinii* pneumonia. *JAMA* 2001; 286: 2450–2460.
59. Thomas CF Jr, Limper AH. *Pneumocystis* pneumonia. *N Engl J Med* 2004; 350: 2487–2498.
60. Edman JC, Kovacs JA, Masur H, *et al.* Ribosomal RNA sequence shows *Pneumocystis carinii* to be a member of the fungi. *Nature* 1988; 334: 519–522.
61. Fei MW, Kim EJ, Sant CA, *et al.* Predicting mortality from HIV-associated *Pneumocystis* pneumonia at illness presentation: an observational cohort study. *Thorax* 2009; 64: 1070–1076.
62. Gal AA, Plummer AL, Langston AA, *et al.* Granulomatous *Pneumocystis carinii* pneumonia complicating hematopoietic cell transplantation. *Pathol Res Pract* 2002; 198: 553–558.
63. Limper AH, Offord KP, Smith TF, *et al. Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. *Am Rev Respir Dis* 1989; 140: 1204–1209.
64. Wang Y, Doucette S, Qian Q, *et al.* Yield of primary and repeat induced sputum testing for *Pneumocystis jiroveci* in human immunodeficiency virus-positive and -negative patients. *Arch Pathol Lab Med* 2007; 131: 1582–1584.
65. Jacobs JA, Dieleman MM, Cornelissen EI, *et al.* Bronchoalveolar lavage fluid cytology in patients with *Pneumocystis carinii* pneumonia. *Acta Cytol* 2001; 45: 317–326.
66. Tasaka S, Hasegawa N, Kobayashi S, *et al.* Serum indicators for the diagnosis of *Pneumocystis* pneumonia. *Chest* 2007; 131: 1173–1180.
67. Limper AH, Knox KS, Sarosi GA, *et al.* An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med* 2011; 183: 96–128.
68. De Stefano JA, Myers JD, Du Pont D, *et al.* Cell wall antigens of *Pneumocystis carinii* trophozoites and cysts: purification and carbohydrate analysis of these glycoproteins. *J Eukaryot Microbiol* 1998; 45: 334–343.
69. Kottom TJ, Limper AH. Cell wall assembly by *Pneumocystis carinii*. Evidence for a unique gsc-1 subunit mediating β-1,3-glucan deposition. *J Biol Chem* 2000; 275: 40628–40634.
70. Armstrong-James D, Stebbing J, John L, *et al.* A trial of caspofungin salvage treatment in PCP pneumonia. *Thorax* 2011; 66: 537–538.
71. Bozzette SA, Sattler FR, Chiu J, *et al.* A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med* 1990; 323: 1451–1457.
72. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. *Chest* 1998; 113: 1215–1224.
73. De Castro N, Neuville S, Sarfati C, *et al.* Occurrence of *Pneumocystis jiroveci* pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. *Bone Marrow Transplant* 2005; 36: 879–883.
74. Masur H, Kovacs JA. Treatment and prophylaxis of *Pneumocystis carinii* pneumonia. *Infect Dis Clin North Am* 1988; 2: 419–428.
75. Ledergerber B, Mocroft A, Reiss P, *et al.* Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med* 2001; 344: 168–174.
76. Reid AB, Chen SC, Worth LJ. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. *Curr Opin Infect Dis* 2011; 24: 534–544.
77. Sepkowitz KA. *Pneumocystis carinii* pneumonia without acquired immunodeficiency syndrome: who should receive prophylaxis? *Mayo Clin Proc* 1996; 71: 102–103.
78. Byrd JC, Hargis JB, Kester KE, *et al.* Opportunistic pulmonary infections with fludarabine in previously treated patients with low-grade lymphoid malignancies: a role for *Pneumocystis carinii* pneumonia prophylaxis. *Am J Hematol* 1995; 49: 135–142.
79. Bodro M, Paterson DL. Has the time come for routine trimethoprim-sulfamethoxazole prophylaxis in patients taking biologic therapies? *Clin Infect Dis* 2013; 56: 1621–1628.
80. Kaur N, Mahl TC. *Pneumocystis jiroveci* (*carinii*) pneumonia after infliximab therapy: a review of 84 cases. *Dig Dis Sci* 2007; 52: 1481–1484.
81. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. *Mayo Clin Proc* 1996; 71: 5–13.

82. Hughes WT, Rivera GK, Schell MJ, *et al.* Successful intermittent chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med* 1987; 316: 1627–1632.
83. D'Antonio RG, Johnson DB, Winn RE, *et al.* Effect of folinic acid on the capacity of trimethoprim-sulfamethoxazole to prevent and treat *Pneumocystis carinii* pneumonia in rats. *Antimicrob Agents Chemother* 1986; 29: 327–329.
84. Bygbjerg IC, Lund JT, Hording M. Effect of folic and folinic acid on cytopenia occurring during co-trimoxazole treatment of *Pneumocystis carinii* pneumonia. *Scand J Infect Dis* 1988; 20: 685–686.
85. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis* 1994; 170: 912–917.
86. Sangiolo D, Storer B, Nash R, *et al.* Toxicity and efficacy of daily dapsone as *Pneumocystis jiroveci* prophylaxis after hematopoietic stem cell transplantation: a case–control study. *Biol Blood Marrow Transplant* 2005; 11: 521–529.
87. Colby C, McAfee S, Sackstein R, *et al.* A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as *Pneumocystis carinii* pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 1999; 24: 897–902.
88. Saukkonen K, Garland R, Koziel H. Aerosolized pentamidine as alternative primary prophylaxis against *Pneumocystis carinii* pneumonia in adult hepatic and renal transplant recipients. *Chest* 1996; 109: 1250–1255.
89. Vasconcelles MJ, Bernardo MV, King C, *et al.* Aerosolized pentamidine as *Pneumocystis* prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. *Biol Blood Marrow Transplant* 2000; 6: 35–43.
90. Souza JP, Boeckh M, Gooley TA, *et al.* High rates of *Pneumocystis carinii* pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. *Clin Infect Dis* 1999; 29: 1467–1471.
91. Wheat LJ, Goldman M, Sarosi G. State-of-the-art review of pulmonary fungal infections. *Semin Respir Infect* 2002; 17: 158–181.
92. Ma LL, Mody CH. When there is a fungus among us, what makes it virulent? *Am J Respir Cell Mol Biol* 2002; 26: 273–276.
93. Lortholary O, Nunez H, Brauner MW, *et al.* Pulmonary cryptococcosis. *Semin Respir Crit Care Med* 2004; 25: 145–157.
94. Park BJ, Wannemuehler KA, Marston BJ, *et al.* Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 2009; 23: 525–530.
95. Mirza SA, Phelan M, Rimland D, *et al.* The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. *Clin Infect Dis* 2003; 36: 789–794.
96. Dromer F, Mathoulin S, Dupont B, *et al.* Epidemiology of cryptococcosis in France: a 9-year survey (1985–1993). French Cryptococcosis Study Group. *Clin Infect Dis* 1996; 23: 82–90.
97. Nath DS, Kandaswamy R, Gruessner R, *et al.* Fungal infections in transplant recipients receiving alemtuzumab. *Transplant Proc* 2005; 37: 934–936.
98. Hage CA, Wood KL, Winer-Muram HT, *et al.* Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-α therapy. *Chest* 2003; 124: 2395–2397.
99. Marr KA. *Cryptococcus gattii* as an important fungal pathogen of western North America. *Expert Rev Anti Infect Ther* 2012; 10: 637–643.
100. Dromer F, Mathoulin-Pelissier S, Launay O, *et al.* Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med* 2007; 4: e21.
101. Lortholary O, Poizat G, Zeller V, *et al.* Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. *AIDS* 2006; 20: 2183–2191.
102. Vilchez RA, Linden P, Lacomis J, *et al.* Acute respiratory failure associated with pulmonary cryptococcosis in non-AIDS patients. *Chest* 2001; 119: 1865–1869.
103. Pappas PG, Perfect JR, Cloud GA, *et al.* Cryptococcosis in human immunodeficiency virus-negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001; 33: 690–699.
104. Wu B, Liu H, Huang J, *et al.* Pulmonary cryptococcosis in non-AIDS patients. *Clin Invest Med* 2009; 32: E70–E77.
105. Cebular S, Lee S, Tolaney P, *et al.* Community-acquired pneumonia in immunocompromised patients. Opportunistic infections to consider in differential diagnosis. *Postgrad Med* 2003; 113: 65–66.
106. Aberg JA, Mundy LM, Powderly WG. Pulmonary cryptococcosis in patients without HIV infection. *Chest* 1999; 115: 734–740.
107. Singh N, Alexander BD, Lortholary O, *et al.* Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. *Clin Infect Dis* 2008; 46: e12–e18.
108. Perfect JR, Dismukes WE, Dromer F, *et al.* Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010; 50: 291–322.

Chapter 5

Surgical management of thoracic aspergillosis

Gilbert Massard, Anne Olland, Nicola Santelmo and Pierre-Emmanuel Falcoz

SUMMARY: Thoracic aspergillosis covers a large spectrum of diseases, with several potential surgical implications.

Traditional aspergillomas arise in pre-existing parenchymal cavities or bronchiectasis. There are two clinical variants, defined by clinical presentation, radiological findings and post-operative outcome, referred to as simple and complex aspergilloma. Semi-invasive aspergillosis has an acute onset with lobar pneumonia; subsequently, the lung excavates and a mycetoma appears.

Surgical intervention for invasive aspergillosis may be discussed either to prevent fatal haemoptysis or to resect residual mycotic sequestra. Since the advent of contemporary antifungal drugs, such operations are seldom required.

Pleural aspergillosis is a variant of empyema and needs to be treated as such.

Invasive bronchial aspergillosis in lung transplant recipients and parietal aspergillosis in drug addicts have been reported as case reports.

Whatever the presentation, treatment should be defined on a multidisciplinary basis.

Service de Chirurgie Thoracique, Hôpitaux Universitaires de Strasbourg, Strasbourg, France.

Correspondence: G. Massard, Service de Chirurgie Thoracique, Hôpitaux Universitaires de Strasbourg, F-67091 Strasbourg, France.
Email: gilbert.massard@chru-strasbourg.fr

Eur Respir Monogr 2013; 61: 50–57.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040512
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Thoracic aspergillosis is, by far, the most common fungal disease of lung and pleura in Western Europe, and concerns both immunocompetent and immunocompromised hosts. Its interest for surgeons has gradually increased over the past decades. Traditionally, thoracic aspergillosis has been classified into three categories: 1) the saprophytic infection, leading to fungus balls within parenchymal or pleural cavities; 2) the invasive aspergillosis observed in neutropenic or immunocompromised patients; and 3) the allergic bronchial aspergillosis known as Hinson–Pepys disease [1]. In the classic text books of the 1960s, 1970s, and 1980s, only the saprophytic aspergilloma, also referred to as megamycetoma, was credited with a surgical interest.

During the past two decades, an increasing number of publications have underlined how surgical management may improve the outcome of selected patients with invasive aspergillosis. Furthermore, at least three distinct, new clinical entities have been described: semi-invasive aspergillosis, ulcerative tracheo-bronchitis in transplant recipients, and parietal aspergillosis.

The purpose of this review is to discuss the peculiarities encountered with thoracic aspergillosis and the management of the different categories of this disease throughout its progression.

Classic saprophytic pulmonary aspergilloma

This historic disease should not be considered old fashioned, as ongoing scientific interest can be found in publications during recent years. Surgical resection for aspergilloma patients is renowned to be technically challenging and to convey a huge mortality and morbidity. Therefore, many authors have restricted surgical indications to heavily symptomatic patients, and advocate simple surveillance in asymptomatic patients. Our purpose in this review is to defend an aggressive, surgical management whenever possible, as we believe symptomatic patients need alleviation, and asymptomatic patients need to halt the further progression of their disease. The legitimacy of the latter position is seen to be conditional, *i.e.* operative risk is low in the asymptomatic patient.

Underlying disease

The underlying disease largely conditions the natural history of the disease and post-operative prognosis. Historically speaking, the classic underlying disease was excavated tuberculosis (TB). In such patients, after recovering from the TB infection, the cavitation undergoes a so-called detersion, which involves the shedding of tuberculous granulomas, the gradual evacuation of caseous necrosis and, eventually, the epithelialisation of the cavity. Communication with the bronchial tree enables the inhalation of sporulated/aerosolised fungal material. Localised conditions with a water/steam saturated atmosphere at 37°C (body temperature, pressure, saturated with water vapour (BTPS in a physiologist's terminology)) favour the desporulation and growth of fungal hyphae. As the fungi grows it produces proteolytic enzymes, such as chymotrypsine and catalase, and the fungal ball increases in size, which results in the progressive increase in the size of cavitation, due to slow peripheral erosion, causing haemoptysis by vascular erosion. In chronic infectious diseases, such as TB, there are usually marked changes in the structure of the surrounding lung, with territories of fibrosis, bronchiectasis, and paraseptal emphysema; obliteration of the pleural space with areas of pachypleuritis; enlarged and even calcified lymph nodes; and considerable hypertrophy of the bronchial vessel, being the usual anatomical changes observed. In particular, the bronchial arterial network typically develops anastomoses with intercostal arteries, and branches arising from the subclavian and internal mammary arteries [1].

Other chronic granulomatous diseases, such as sarcoidosis, may lead to the production of a cavity that is associated with marked fibrotic changes of the surrounding lung. Similar changes have also been observed in patients with ankylosing spondylitis (Bechterew's disease). Residual cavities after healing of a lung abscess or a lung infarction add to the spectrum of residual cavitations. Pulmonary hydatidosis can lead to aspergilloma either spontaneously or after surgical removal [2, 3]. Aspergilloma may occur in areas of bullous emphysema or pulmonary sequestration, and is exceptionally observed within excavated tumours [4].

The rapidly increasing use of radiofrequency for the ablation of primary or secondary lung tumours is an important provider of chronic parenchymal cavitations, which may become infected with *Aspergillus* spp. [5].

There is a classical rule that states TB and aspergillosis do not occur simultaneously, but sequentially. However, there are published case reports describing aspergilloma together with allergic aspergillosis, or association of aspergilloma with actinomycosis [6, 7].

Currently, the most common variant of aspergilloma occurs in a healthy looking lung. Pathology describes a thin-walled cavity lined by bronchial mucosa and is interpreted as a localised bronchiectasis. It remains unclear whether this isolated bronchiectasis is cause or consequence of the aspergilloma [1].

Prognostic significance of clinical and radiological classification

In 1960, BELCHER and PLUMMER [8] defined a clinical and radiological classification for aspergilloma that is still valid and used over half a century later. This classification clearly distinguishes between simple and complex aspergilloma.

Simple aspergilloma is characterised by a relatively small-sized mycetoma, embedded in a thin-walled cavitation and surrounded by a normal looking lung without any areas of fibrosis or pleural thickening. These patients have a normal nutritional status, and are asymptomatic, with normal lung functions. This presentation is usually applied to the so-called bronchial aspergilloma.

Conversely, complex aspergilloma usually consists of a larger-sized mycetoma, which is hosted in a thick-walled cavitation with marked parenchymal fibrosis and/or pleural scarring. The complex aspergilloma patients are usually symptomatic (dypnoea, purulent sputum, haemoptysis), have a poor nutritional status and a decreased lung function [1, 9]. The archetype of this category is the patient with cavitary TB.

This classification is also nicely correlated to post-operative outcome. Surgical morbidity, such as intra-operative bleeding, post-operative bleeding, prolonged air leak, the need for a thoracoplasty, and respiratory failure are significantly lower in patients with simple aspergilloma. In our previously published experience, excessive bleeding was seen in 20% of simple aspergillomas, and in 60% of complex aspergillomas; rates for pleural space disease were 20% and 36%, respectively [1]. Except in the incidence of one series [9], there are virtually no post-operative deaths following resection for simple aspergilloma (table 1). These data have been confirmed by a recent publication by CHEN *et al.* [14].

Time trends of aspergilloma

The advent of major anti-TB drugs and national programmes to fight TB has proven efficacy in most European countries. Hence, the prevalence of residual cavitation as a consequence of TB has dramatically decreased during the past three decades. CHATZIMICHALIS *et al.* [15] compared two consecutive periods and demonstrated a decrease of cavitary TB in the most recent period, which correlated with a decrease in the number of complex aspergilloma cases (table 2). Subsequently, there has been a dramatic improvement in post-operative outcomes in recent years. An updated study by LEJAY *et al.* [16] confirms the reduction in the number of complex aspergilloma cases and the more favourable post-operative outcome for such patients that undergo surgery as a result of their illness. However, due to the progressive expansion of the European Union, and with it the increase in migration from areas that have a marked prevalence for TB, a significant proportion of patients with complex aspergilloma will still occur.

Surgical decision making

The choice of an adequate procedure is of paramount importance. The ideal treatment consists of the resection of both the mycetoma and the underlying cavity. Lobectomy is, therefore, the option of choice [1, 9, 13]. Segmentectomy is subjected to a higher incidence of prolonged air leak, and may favour intra-operative disruption of the cavitation and pleural seeding. Pneumonectomy carries a prohibitive risk for empyema and/or bronchial fistula and should be avoided wherever possible [17]. During the recent decade, the video-assisted thoracoscopic surgery (VATS) approach has progressively become the gold standard replacing open lobectomy for both small

Table 1. Comparative operative mortality following resection of simple and complex aspergilloma

First author [ref.]	Patients n	Mortality %	
		Simple aspergilloma	Complex aspergilloma
BATTAGLINI [10]	15	0	18.1
DALY [9]	53	4.7	34.3
STAMATIS [11]	29	0	11.7
SHIRAKUSA [12]	24	0	0
MASSARD [1]	63	0	10
REGNARD [13]	87	0	6.2

sized tumours and benign diseases. As such, there are several short series demonstrating both feasibility and safety for VATS lobectomy for aspergilloma [18–20]. Careful review of computed tomography (CT) scans enables the surgeon to choose adequately between VATS or the open approach in complex cases [20].

Table 2. Demographic and post-operative data comparing two chronological subsets of patients

	Year range	
	1974–1991	1992–1997
Mean age years	49	46
Tuberculosis	57.4	16.6
Complex aspergilloma	80	41.6
Excessive bleeding	44.1	8.3
Prolonged air leak	47	16.6
Hospital stay >30 days	32.3	8.3

Data are presented as percentage unless otherwise stated. Data taken from [15].

This ideal surgical management may not be applicable in patients with complex aspergilloma, either because lung function and/or involvement of the fissure preclude lobectomy. We have advocated, for such patients, a direct approach with an incision of the cavitation and removal of the fungal material, followed by obliteration of the cavitation with a thoracoplasty [1, 21]. Such a strategy leads to excellent medium-term results with permanent cure and a negative serodiagnosis, but the price to pay is a significant operative mortality rate that is close to 10% [1]. An alternative to thoracoplasty is plombage with a muscle flap; however, the latter may be limited by malnutrition or transection of the muscles during previous thoracotomies [22]. The ultimate, least invasive options, are represented either by simple cavernostomy, which is feasible if close to the chest wall, or intra-cavity administration of antifungal drugs [23]. Some case reports have shown that, on occasion, a bronchoscopic removal of the mycetoma has been possible [24]. However, we need to be aware that the recurrence of the mycetoma is likely as long as the cavitation persists.

Can we reduce blood loss during surgery of complex aspergilloma? Several attempts have been described to anticipate the control of bleeding with selective embolisation of the bronchial arteries, but these have not been conclusive. As a matter of fact, the rather anarchic collateral circulation is beyond endovascular control.

We should add a word of caution regarding antifungal therapy. It is well established that the fibrous and avascular walls of the cavitation effectively oppose penetration of antifungal drugs into the fungus ball. Hence, pre-operative treatment makes no sense. Whenever the lesion has been completely resected, without intra-operative spillage, there is no reason to begin the patient on antifungal therapy post-operatively [25].

The final question is when to operate on a patient? Should we accept an operative risk and go for a prophylactic surgery in asymptomatic patients, although the natural history of the disease is unpredictable? Or should we limit surgery to only heavily symptomatic patients, knowing that the morbidity will be particularly high in patients operated on in emergency conditions? In our reasoning the answers are rather obvious.

Asymptomatic patients usually present with simple aspergilloma, hence post-operative outcome is benign, and these patients are definitely eligible for a minimally invasive resection. As such, surgery is completely justified in asymptomatic patients.

Unfortunately in symptomatic patients we are most often faced with the challenging problem of complex aspergilloma. However, symptoms usually dictate an active intervention. In this category, experience of the surgical team and multidisciplinary discussion are of paramount importance to select the appropriate procedure: anatomic resection, removal of fungus ball and thoraco-/myoplasty, or a lesser procedure in critically ill patients.

Pleural aspergilloma

Pleural aspergilloma is an exceptional disease and seldom addressed in the literature [1]. There are two possible presentations, as follows. 1) Early post-operative aspergilloma, which presents as a

post-operative empyema that is declared during the first 4–6 weeks after an operation. This usually occurs in patients who undergo surgery for aspergilloma and who show a prolonged air leak. The most probable mechanism is intra-operative seeding. 2) Late post-operative pleural aspergilloma, which occurs months or even years following a parenchymal resection and usually develops in a residual pleural space. For both presentations of pleural aspergilloma to occur, the presence of a small bronchopleural fistula is required in order to carry aerosolised fungal spores towards the cavity.

Treatment of such patients is tedious. They are usually in poor general condition and present with invalidating symptoms. Decortication is advisable only in patients who did not undergo any parenchymal resection, because previous partial lung resection precludes complete obliteration of the pleural cavity by re-expansion of the residual lung. When loss of parenchymal volume is obvious, thoracoplasty remains the only surgical option. Muscle transfers are likely to fail because of previous thoracotomy and poor nutritional status. Owing to the poor nutritional and functional status of such patients, there is a higher rate of complication. In a personal series of 13 patients, two died post-operatively, nine experienced excessive bleeding and eight required prolonged drainage. Hospital stay was in excess of 30 days for nine patients [2]. According to GUAZZELLI *et al.* [26], penetration of antifungal drugs into the pleural cavity is reliable, and antifungal therapy makes sense prior to surgical management.

Semi-invasive aspergillosis

Semi-invasive aspergillosis is seldom referred to, although many centres have anecdotal experience of such patients [27]. This disease occurs preferentially in patients with previous radiation therapy. The onset mimics an acute lobar pneumonia with a high fever, which does not respond to antibiotics. After 2–3 weeks, a cavitation appears in the previously fibrosed lung. Fever recedes, and progressively the radiological appearance suggests a complex aspergilloma. Disabling symptoms eventually leads to surgical discussion.

Patients developing semi-invasive aspergillosis after previous lobectomy and radiation therapy represent a particular subset. Territories of radiation pneumonitis are particularly prone to acute *Aspergillus* pneumonia. In such patients, completion pneumonectomy, following previous lobectomy and radiation therapy, would have a tremendous risk owing to pleural adhesions and hilar fibrosis; operative mortality may reach 25% [28]. The most valuable option is the removal of the fungal material followed by a thoracoplasty, which may be completed with muscle plombage if available [22].

Invasive aspergillosis

Invasive aspergillosis accounts for 30% of all fungal infections in patients with leukaemia; at least 5% of patients treated with leukaemia will develop invasive aspergillosis. Prevalence increases to 70% if neutropenia exceeds 34 days. Mortality is high despite early antifungal treatment; the overall mortality rates are 50% during neutropenia, and in excess of 90% after bone marrow graft. While it has been estimated that approximately 15% of all patients with invasive aspergillosis could be subjected to surgical care [29], we believe that the advent of more potent antifungal drugs, such as voriconazole and capsifungine, has considerably reduced the need for surgery in such patients [30].

Natural history of the disease and diagnosis

The onset of invasive aspergillosis usually occurs during neutropenia. Fungal hyphae invade pulmonary vessels and determine peripheral infarctions. At this stage, a CT scan would reveal a rounded opacity surrounded by a low-density halo [29, 31], whereas a bone marrow sample would show neutrophils colonising the infarcted areas and causing tissular necrosis, a phenomena that

triggers the appearance of the air-crescent sign on radiographs. Necrosis may lead to haemoptysis, especially when occurring close to the major branches of the pulmonary artery.

In a patient receiving chemotherapy, any three of the following items may be suggestive of invasive aspergillosis: neutropenia, pneumonia, haemoptysis, persistent fever despite antibiotics, chest pain, halo sign and/or air crescent sign [29].

Noninvasive diagnosis relies on the detection of *Aspergillus* antigens and the culture of *Aspergillus* from bronchoalveolar lavage fluid. Although identification of antigen is correlated to a strong positive predictive value exceeding 90%, lavage is negative for antigens in more than 50% of patients [32].

Rationale of surgical management

Surgical management may be indicated to serve two purposes. 1) To prevent massive haemoptysis [31]. In this situation, radiological surveillance has shown a necrotic lesion close to a major vessel. An operation is undertaken in an emergency situation in patients who may not have completely recovered their bone marrow function. In a series that included eight patients who were operated on during aplasia, there were no operative deaths; however aspergillosis recurred and caused death in two of the patients [31]. 2) To prevent re-infection during subsequent chemotherapy [29]. In this situation, an elective operation is scheduled to remove the mycotic sequestra, which would be a source for re-infection during a subsequent neutropenia. Such operations are planned once the patient has recovered their normal bone marrow function. Several reports describe successful bone marrow transplantations after such procedures. Operative risk is at an acceptable level with a mortality rate less than 10%. Medium-term results in terms of aspergillosis are acceptable with a recurrence rate less than 10% (table 3).

The basic principle of such operations is to use parenchyma-sparing resections, similarly to surgery for pulmonary metastases. Pneumonectomy should be avoided, because of the high risk of lethal complications that threatens the pneumonectomy made in emergency situations. However, as stated previously, contemporary antifungal drugs have considerably decreased the need for operative management of the disease.

Aspergillus bronchitis

This entity has been described in a short series of heart–lung graft recipients reported by the Stanford group[37]. The usual presentation is an ulcerative tracheobronchitis with abundant fibrin deposits, located in the immediate vicinity of the airway anastomosis and in the proximal segment of the donor airway. Microbiological analysis of the fibrin deposits identifies high concentrations of fungal hyphae. One-third of the patients progressed to a fatal invasive aspergillosis [37]. Therefore, early and aggressive treatment is mandatory. A case report, by KESSLER *et al.* [38], showed a patient with *Aspergillus* bronchitis, following a right single-lung

Table 3. Operative mortality and relapse of aspergillosis following surgery

First author [ref.]	Patients	Operative mortality	Relapse aspergillosis
BARON [29]	12	0	1
BERNARD [31]	7	0	0
LUPINETTI [33]	6	1	3
ROBINSON [34]	16	5	1
WONG [35]	16	1	0
YOUNG [36]	8	0	NA

Data are presented as n. NA: not available.

transplant, succumbed to a bronchoarterial fistula, which resulted from erosion by a peribronchial fungal abscess [38].

Parietal aspergillosis

This rare condition has been reported in isolated case reports [39, 40]. These patients presented with a parietal abscess at the site of a central venous line or sternal osteomyelitis. All patients recovered with antifungal treatment after surgical debridement.

Conclusion

Aspergillus may cause a wide spectrum of diseases within the chest. Adequate management requires knowledge of the possibilities of surgical management. Management of these, often complicated, patients should be routinely discussed on a multidisciplinary basis. Surgery is still the leading treatment in cases of classic saprophytic aspergilloma and semi-invasive aspergilloma. In all other variants described here, contemporary antifungal drugs have more or less banned the need for surgery.

Statement of Interest

G. Massard has received payment for a lecture on mini-invasive surgery for lung cancer at a national event in France, from Sanofi-Aventis, in December 2012. N. Santelmo has provided expert testimony to Intuitive Surgical Robot da Vinci proctoring.

References

1. Massard G, Roeslin N, Wihlm JM, *et al.* Pleuropulmonary aspergilloma: clinical spectrum and results of surgical treatment. *Ann Thorac Surg* 1992; 54: 1159–1164.
2. Bal A, Bagai M, Mohan H, *et al.* Aspergilloma in a pulmonary hydatid cyst: a case report. *Mycoses* 2008; 51: 357–359.
3. Vasquez JC, Montesinos E, Rojas L, *et al.* Surgical management of *Aspergillus* colonization associated with lung hydatid disease. *Ann Thorac Cardiovasc Surg* 2008; 14: 116–118.
4. Liu HS, Li SQ, Qin YZ, *et al.* Surgical treatment of intralobar pulmonary sequestration. *Chin Med Sci J* 2010; 25: 53–56.
5. Hiraki T, Gobara H, Mimura H, *et al.* Aspergilloma in a cavity formed after percutaneous radiofrequency ablation for lung cancer. *J Vasc Interv Radiol* 2009; 20: 1499–1500.
6. Huang CW, Lee MA, Lu RH, *et al.* A case of pulmonary aspergilloma and actinomycosis. *J Med Microbiol* 2011; 60: 543–546.
7. Montani D, Zendah I, Achouh L, *et al.* Association of pulmonary aspergilloma and allergic bronchopulmonary aspergillosis. *Eur Respir Rev* 2010; 19: 349–351.
8. Belcher JR, Plummer NS. Surgery in bronchopulmonary aspergillosis. *Br J Dis Chest* 1960; 54: 335–341.
9. Daly RC, Pairolero PC, Piehler JM, *et al.* Pulmonary aspergilloma. Results of surgical treatment. *J Thorac Cardiovasc Surg* 1986; 92: 981–988.
10. Battaglini JW, Murray GF, Keagy BA, *et al.* Surgical management of symptomatic pulmonary aspergilloma. *Ann Thorac Surg* 1985; 39: 512–516.
11. Stamatis G, Greschuchna D. Surgery for pulmonary aspergilloma and pleural aspergillosis. *Thorac Cardiovasc Surg* 1988; 36: 356–360.
12. Shirakusa T, Ueda H, Suito T, *et al.* Surgical treatment of pulmonary aspergilloma and *Aspergillus* empyema. *Ann Thorac Surg* 1989; 48: 779–782.
13. Regnard JF, Icard P, Nicolisi M, *et al.* Aspergilloma: a series of 89 surgical cases. *Ann Thorac Surg* 2000; 69: 898–903.
14. Chen QK, Jiang GN, Ding JA. Surgical treatment for pulmonary aspergilloma: a 35-year experience in the Chinese population. *Interact Cardiovasc Thorac Surg* 2012; 15: 77–80.
15. Chatzimichalis A, Massard G, Barsotti P, *et al.* Surgery for aspergilloma: a reappraisal. *Ann Thorac Surg* 1998; 65: 927–929.
16. Lejay A, Falcoz PE, Santelmo N, *et al.* Surgery for aspergilloma: time trend towards improved results? *Interact Cardiovasc Thorac Surg* 2011; 13: 392–395.
17. Massard G, Dabbagh A, Wihlm JM, *et al.* Pneumonectomy for chronic infection is a high risk procedure. *Ann Thorac Surg* 1996; 62: 1033–1037.

18. Parker KL, Zervos MD, Darvishian F, *et al.* Video-assisted thoracoscopic lobectomy for pulmonary aspergilloma after life-threatening hemoptysis in a patient with lupus. *Ann Thorac Surg* 2010; 89: 291–292.
19. Ichinose J, Kohno T, Fujimori S. Video-assisted thoracic surgery for pulmonary aspergilloma. *Interact Cardiovasc Thorac Surg* 2010; 10: 927–930.
20. Yen YT, Wu MH, Cheng L, *et al.* Image characteristics as predictors for thoracoscopic anatomic lung resection in patients with pulmonary tuberculosis. *Ann Thorac Surg* 2011; 92: 290–295.
21. Igai H, Kamiyoshihara M, Nagashima T, *et al.* Pulmonary aspergilloma treated by limited thoracoplasty with simultaneous cavernostomy and muscle transposition flap. *Ann Thorac Cardiovasc Surg* 2012; 18: 472–474.
22. Grima R, Krassas A, Bagan P, *et al.* Treatment of complicated pulmonary aspergillomas with cavernostomy and muscle flap: interest of concomitant limited thoracoplasty. *Eur J Cardiothorac Surg* 2009; 36: 910–913.
23. Cesar JM, Resende JS, Amaral NF, *et al.* Cavernostomy x resection for pulmonary aspergilloma: a 32-year history. *J Cardiothorac Surg* 2011; 6: 129–135.
24. Stather DR, Tremblay A, MacEachern P, *et al.* Bronchoscopic removal of a large intracavitary pulmonary aspergilloma. *Chest* 2013; 143: 238–241.
25. Sagan D, Gozdziuk K. Surgery for pulmonary aspergilloma in immunocompetent patients: no benefit from adjuvant antifungal pharmacotherapy. *Ann Thorac Surg* 2010; 89: 1603–1610.
26. Guazzelli LS, Severo CB, Hoff LS, *et al.* Bola fúngica por *Aspergillus fumigatus* em cavidade pleural. [*Aspergillus fumigatus* fungus ball in the pleural cavity.] *J Bras Pneumol* 2012; 38: 125–132.
27. Kibbler CC, Milkins SR, Bhamra A, *et al.* Apparent pulmonary mycetoma following invasive aspergillosis in neutropenic patients. *Thorax* 1988; 43: 108–112.
28. McGovern EM, Trastek VF, Pairolero PC, *et al.* Completion pneumonectomy: indications, complications and results. *Ann Thorac Surg* 1988; 46: 141–146.
29. Baron O, Guilaumé B, Moreau P, *et al.* Aggressive surgical management in localized pulmonary mycotic and nonmycotic infections for neutropenic patients with acute leukemia. *J Thorac Cardiovasc Surg* 1998; 115: 63–69.
30. Herbrecht R, Denning DW, Patterson TF, *et al.* Voriconazole *versus* amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.
31. Bernard A, Caillot D, Couailler JF, *et al.* Surgical management of pulmonary aspergillosis in neutropenic patients. *Ann Thorac Surg* 1997; 64: 1441–1447.
32. Saito H, Anaissie EJ, Morice RC, *et al.* Bronchoalveolar lavage in the diagnosis of pulmonary infiltrates in patient with acute leukemia. *Chest* 1988; 94: 745–749.
33. Lupinetti FM, Behrendt DM, Giller RH, *et al.* Pulmonary resection for fungal infection in children undergoing bone marrow transplantation. *J Thorac Cardiovasc Surg* 1992; 104: 684–687.
34. Robinson LA, Reed EC, Galbraith TA, *et al.* Pulmonary resection for invasive *Aspergillus* infections in immunocompromised patients. *J Thorac Cardiovasc Surg* 1995; 109: 1182–1196.
35. Wong K, Waters CM, Walesby RK. Surgical management of invasive pulmonary aspergillosis in immunocompromised patients. *Eur J Cardiothorac Surg* 1992; 6: 138–142.
36. Young VK, Maghur HA, Luke DA, *et al.* Operation for cavitating invasive pulmonary aspergillosis in immunocompromised patients. *Ann Thorac Surg* 1992; 53: 621–624.
37. Kramer MR, Denning DW, Marshall SE, *et al.* Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis* 1991; 144: 552–556.
38. Kessler R, Massard G, Warter A, *et al.* Bronchial-pulmonary artery fistula after unilateral lung transplantation: a case report. *J Heart Lung Transplant* 1997; 16: 674–677.
39. Walker WA, Pate JW. Primary *Aspergillus* osteomyelitis of the sternum. *Ann Thorac Surg* 1991; 52: 868–870.
40. Buescher TM, Moritz DM, Killyon GW. Resection of chest wall and central veins for invasive cutaneous *Aspergillus* infection in an immunocompromised patient. *Chest* 1994; 105: 1283–1285.

Chapter 6

Surgical treatment of invasive aspergillosis

Adelheid End[*], *Birgit Willinger*[#] *and Oliver A. Cornely*[¶]

SUMMARY: Invasive pulmonary aspergillosis (IPA) is encountered in immunocompromised or neutropenic patients presenting with a high mortality rate. A high index of suspicion is necessary in patients with risk factors such as haematopoietic stem cell transplantation and solid organ transplantation. Radiological imaging is the cornerstone in diagnosing IPA. Modern antifungal therapy with voriconazole and liposomal amphotericin B plays a major role. In selected patients, surgery may be necessary to prevent massive haemoptysis or to prevent re-infection during subsequent chemotherapy. Parenchyma-sparing surgery with open wedge resections or thoracoscopic procedures is recommended, whereas pneumonectomy has a high mortality and is only indicated in emergency situations. In carefully selected patients and with excellent interdisciplinary management, surgery can be performed with low operative morbidity and with a beneficial effect on disease control and survival. Prognosis of IPA is strongly influenced by the underlying disease.

[*]Dept of Thoracic Surgery, Medical University of Vienna, and
[#]Dept of Laboratory Medicine, Division of Clinical Microbiology, Medical University of Vienna, Vienna, Austria.
[¶]Dept I of Internal Medicine, University Hospital of Cologne, Cologne, Germany.

Correspondence: A. End, Dept of Thoracic Surgery, Medical University of Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria.
Email: adelheid.end@meduniwien.ac.at

Eur Respir Monogr 2013; 61: 58–65.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040712
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Invasive pulmonary aspergillosis (IPA) is an increasingly common opportunistic fungal infection in immunocompromised patients and accounts for a large number of mortalities due to fungi in haematological and solid organ transplantation [1]. The incidence, clinical presentation, natural history of disease and rationale of surgical management of aspergillosis, especially of the simplex and complex aspergilloma, are addressed by MASSARD *et al.* [2] in another chapter of this issue of the *European Respiratory Monograph* (*ERM*), and the medical treatment is presented by BASSETTI and RIGHI [3], also in this issue of the *ERM*. The purpose of the current chapter is to give an overview of the most important items and surgical aspects of IPA.

Risk factors and clinical presentation

The major risk factors for IPA are inherited immunodeficiency, prolonged neutropenia, haematopoietic stem cell transplantation and solid organ transplantation, especially lung and heart/lung transplantation. The lungs are involved in about 85% of cases with invasive aspergillosis. *Aspergillus* may also disseminate to other organs, including the brain [1]. There are also increasing numbers of IPA in patients with severe chronic obstructive pulmonary disease and critically ill patients [3, 4]. An early diagnosis is crucial to improve prognosis. In neutropenic

patients without adequate therapy, IPA will almost always progress to fatal pneumonia, which is characterised by haemorrhagic infarction or necrotising pneumonia [1]. The symptoms of IPA are nonspecific and usually mimic bronchopneumonia with fever unresponsive to antibiotics. Chest pain and haemoptysis may be present. In neutropenic patients, IPA is one of the most common causes of haemoptysis [5].

Nonradiological diagnosis

Early diagnosis is paramount to reduce mortality and morbidity. In the high-risk patient with clinical signs and symptoms suspicious for IPA, a high-resolution computed tomography (CT) or magnetic resonance imaging scan, serum biomarkers (*e.g.* *Aspergillus* galactomannan (GM) and serum 1,3-β-D-glucan), sputum examination, bronchoalveolar lavage (BAL) fluid examination and tissue biopsy for histopathology and culture of micro-organisms are helpful in the diagnosis. The currently available laboratory methods for diagnosing invasive aspergillosis include microscopic detection, isolation of the fungus, detection of antigen or histopathological evidence of invasion [6]. For definite diagnosis of proven invasive aspergillosis, histological and cultural evidence from biopsies, resection material or other specimens obtained from normally sterile body sites is required (fig. 1). However, it is not always possible to fulfil these criteria and a combination of different methods is necessary to detect and identify the fungal organism causing the disease.

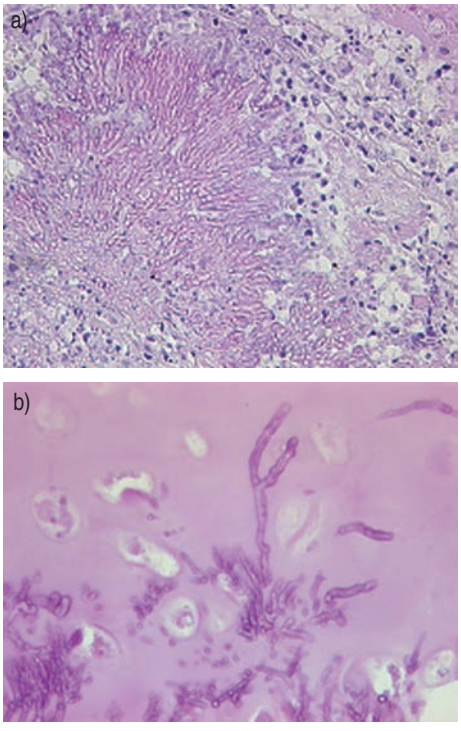


Figure 1. a) Histology of invasive pulmonary aspergillosis. b) Progressive acute angle dichotomous branching of *Aspergillus* hyphae.

The most commonly used antigen test for *Aspergillus* detection is the double-sandwich ELISA test Platelia Aspergillus (Bio-Rad Laboratories, Marnes, France), which is validated for use in serum and BAL fluid and has been evaluated in oncohaematological patients and those receiving haematopoietic precursors who have prolonged neutropenia. The combination of a high-risk patient with suggestive clinical and radiological (CT scan) findings and a positive serum GM may be considered adequate for a diagnosis of ''probable'' IPA. However, it has to be kept in mind that solely testing for antigenaemia does not replace other tests for IPA. The sensitivity of serological antigen testing depends on the severity of disease.

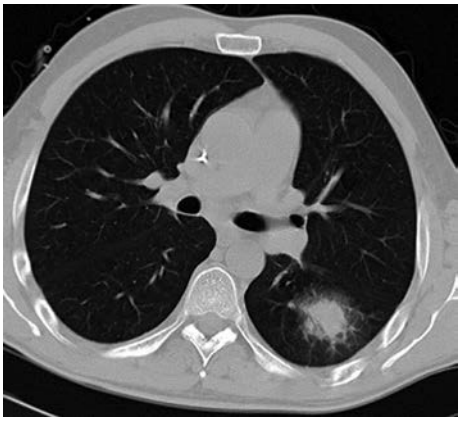


Figure 2. Thoracic computed tomography scan with a mass in the left lower lobe surrounded by a zone of ground-glass attenuation (''halo sign'').

Bronchoscopy with BAL is an established method for the diagnosis of infections; the sensitivity for detecting IPA increases with multiple cultures and direct microscopy of BAL [7]. *Aspergillus* GM antigen for IPA can be detected at a mean of 8 days before diagnosis by other means. PCR may be useful to exclude *Aspergillus* infection [8]. Transbronchial biopsy is an established method in the diagnosis of IPA in immunocompromised patients but requires a

Table 1. Indications for surgery in invasive pulmonary aspergillosis (IPA)

Haemoptysis
Planned immunosuppression
Failure of antifungal therapy
Early-stage IPA
Localised or multilocular IPA

thrombocyte count of about 50 000 cells·μL^{-1} to avoid bleeding. This is also the case in CT-guided percutaneous lung biopsy, which carries a high risk of pneumothorax. Open lung biopsy is not advised in pancytopenic patients because of the high rate of post-operative complications.

Radiological diagnosis

Radiological imaging is the cornerstone in diagnosing IPA. IPA is often treated in clinical practice on the appearance of typical radiological signs, even in the absence of any microbiological or histological evidence. Lesions with imaging suggestive of aspergillosis are lung sequestra on plain radiograph or CT, the "halo sign" lesion on CT scan, and cavitating lesions [9]. These focal lesions are amenable to surgery, which is the best way to confirm the diagnosis. Only in patients with a high suspicion of tumour and negative bronchoscopy may CT-guided biopsy be considered as a second-line diagnostic procedure.

The halo sign is considered early evidence of pulmonary aspergillosis even before serological tests become positive, and it warrants the administration of antifungal therapy (fig. 2). The air crescent sign indicates the development of tissue necrosis and develops mainly from larger consolidations or masses. The new appearance of pulmonary consolidation or infiltrates in a neutropenic patient with antibiotic resistant fever is already suspicious of IPA [8, 10, 11].

Ulcerative tracheobronchitis is seen at the anastomotic site of lung transplant recipients and may lead to IPA in 30% of patients [12, 13], but may also occur in nontransplant patients. Early and aggressive treatment is necessary [2]. Voriconazole is recommended as the initial therapy. Bronchoscopic evaluation is the most important aspect of diagnosis; CT will assess the lack of progression in its initial stages [1].

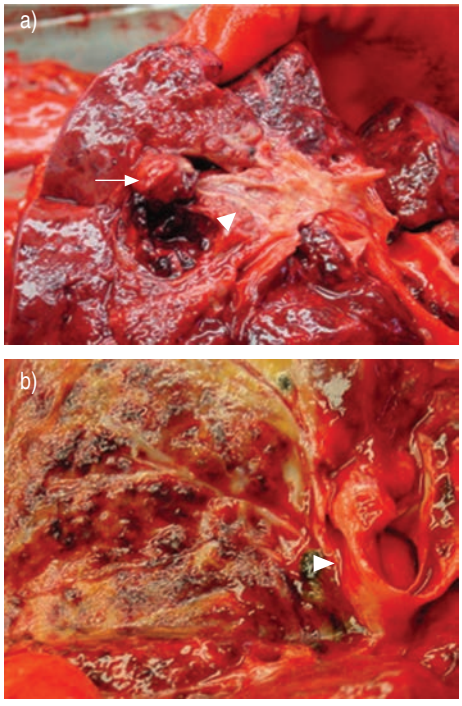


Figure 3. a) Fatal haemoptysis caused by invasive pulmonary aspergillosis. Pulmonary nodule (arrow) and erosion of the pulmonary artery (arrowhead) at autopsy. b) Detailed view of erosion of the pulmonary artery (arrowhead).

Medical treatment

Early initiation of antifungal therapy in patients with strongly suspected invasive aspergillosis is warranted while a diagnostic evaluation is conducted. Voriconazole and liposomal amphotericin B are first-line antifungal agents [1, 3]. Initial therapy with voriconazole has led to better responses and improved survival and resulted in fewer side-effects than amphotericin B [14]. However, voriconazole is limited by numerous drug interactions. In highly immunocompromised patients, liposomal amphotericin B has proven to be effective with standard dosing [15]. Echinocandins, such as caspofungin, and several new classes of antifungals enlarge the therapeutic armamentarium.

Empirical therapy has to be started as soon as infection is suspected, *i.e.* upon prolonged fever in high-risk patients. Pre-emptive therapy is started when IPA is suspected due to lesions in the CT scan or detection of antigen, in order to decrease mortality.

A successful course of voriconazole may preclude the need for surgical resection. Using secondary antifungal prophylaxis after initial successful primary therapy prior to stem cell transplantation in patients with prior

invasive aspergillosis suggests that antifungal therapy alone may be effective [16]. However, early surgical evaluation and close CT monitoring is required during medical therapy, in order to intervene if a lesion further encroaches upon a critical structure [1].

Surgical treatment

In comparison to the classic saprophytic pulmonary aspergilloma, surgical resection has a limited role in the management of patients with IPA [2]. Decisions concerning surgery should be individualised in order to account for a number of variables, such as degree of resection, unilateral *versus* bilateral lesions, comorbidities, performance status, the goal of antineoplastic therapy (*e.g.* curative *versus* palliative), and potential impact of delays in chemotherapy. If the predicted survival due to uncontrolled haematological disease is less than 3 months, (non-surgical) treatment should be applied according to individual needs [9].

Indications for surgery

The indications for surgery are summarised in table 1. Surgery in early-stage IPA is preferred. Single localised lesions as well as multiple lesions can potentially be resected.

Treatment of haemoptysis

The most important indication is treatment of life-threatening haemoptysis.

Table 2. Surgical procedures for invasive pulmonary aspergillosis [2, 24, 25]

First author [ref.]	Year	Patients n	Underlying disease	Procedures	Post-operative mortality	Post-operative complications	Recurrence of *Aspergillus*
LUPINETTI [21]	1992	6	Haematological (paediatric)	3 lob, 3 wedge (1 mult, 2 bilat)	1	NA	3
YOUNG [26]	1992	8	Haematological	7 lob, 1 wedge (mult)	0	0	NA
WONG [17]	1992	16	Haematological	15 lob, 1 pneum	1	0	0
MOREAU [27]	1993	6	Haematological, chemotherapy	6 lob	0	0	0
ROBINSON [18]	1995	16	Haematological (n=14), liver transplant (n=2)	9 lob, 1 bilob, 4 wedge, 2 pneum	5 (at days 7, 11, 20, 20 and 28)	9 (2 prolonged air leak)	1
BERNARD [23]	1997	7#	Haematological (paediatric n=1)	4 lob, 1 lingulectomy, 2 wedge (VATS)	0	1 haemorrhage (re-thoracotomy)	0
SALERNO [28]	1998	13	Haematological	3 lob, 10 wedge (5 mult, 1 chest wall)	1 (at day 2)	1 empyema, 1 haemothorax	4
BARON [11]	1998	12¶	Haematological	Pneum, lob, bilob, wedge¶	0	0	1
YEGHEN [9]	2000	37+	Haematological	4 partial lob, 11 mult lob/segm, 20 lob, 2 pneum	0§	3 haemorrhage, 1 re-thoracotomy, 1 wound infection, 1 nonfungal chest infection	3 proven, 4 suspected
GOW [29]	2003	18	Haematological (paediatric)	13 wedge, 3 lob, 2 pneum (16 thoracotomy, 2 VATS)	0f	0	6 (5 unknown)

Lob: lobectomy; wedge: wedge resection; mult: multiple; bilat: bilateral; pneum: pneumonectomy; bilob: bilobectomy; VATS: video-assisted thoracoscopic surgery; chest wall: chest wall resection; segm: segmental resection; NA: not available. #: 8 other patients had emergency surgery; ¶: 12 out of 18 patients proved to have an *Aspergillus* infection (the total included 1 pneum, 4 bilob, 7 lob and 6 wedge); +: 35 histologically confirmed invasive pulmonary aspergillosis; §: 8 deaths (at days 1–28) due to *Aspergillus* infection; f: 3 deaths (at days 6–21).

Table 3. Post-operative risks of surgery in invasive pulmonary aspergillosis [8]

Event	Risk %
Peri-operative mortality	10–14
Post-operative complications	7–10
Recurrent fungal infection	10–16

Haemoptysis is a serious complication, and may occur during profound pancytopenia or upon recovery from neutropenia. Massive haemoptysis requires emergency surgery even if the patient is neutropenic or thrombocytopenic [2, 17–20] (fig. 3). Persistent haemoptysis from a single cavitary lesion warrants its resection. Other measures to reduce haemoptysis include embolisation of involved blood vessels; however, recurrence of bleeding is possible [1]. The decision to embolise or to operate is based on the degree of bleeding and the experience of interventional radiologists and surgeons.

Reduce infection

The second most important indication is to eradicate a localised infection and to minimise the risk of re-infection. In patients with residual localised lesions, surgery is indicated if immunosuppression (bone marrow transplantation or aggressive chemotherapy) is being continued, or prior to subsequent intense chemotherapy and bone marrow transplantation [1, 21, 22]. Surgical resection can provide a definitive diagnosis.

Treatment of lesions

In pulmonary lesions contiguous with the great vessels or the pericardium, surgery has to be discussed to prevent erosion of vessels and penetration into the pericardial space. Radiological monitoring is essential for early detection of the halo sign. Disappearance of the perivascular fat rim alerts attention, since it precedes disruption [23]. Surgical therapy may also be useful in patients with lesions invading the chest wall, in order to relieve pain and prevent pleurocutaneous fistula.

Surgical procedures

The surgical procedures for IPA are summarised in table 2, and encompass parenchyma-saving resections similar to those used in surgery for pulmonary metastases, such as open wedge resections or video-assisted thoracoscopic surgery (VATS) procedures. Lobectomies are performed for larger lesions, multiple lesions in one lobe and centrally located lesions. Multiple wedge resections can be performed for multilocular IPA [28, 30], and re-operations are possible if required [29]. Pneumonectomies should be avoided whenever possible because they carry a high risk of mortality and post-operative complications [31]. In most series, thoracotomy is the most frequent access; VATS is limited to smaller peripheral lesions [19, 24, 29]. Elective parenchyma-saving procedures are efficient and safe, and have to be combined with adequate antifungal therapy. Good peri-operative management, including platelet transfusions before and during surgery, is pre-requisite.

Complications

Post-operative survival has increased to 80%, with few surgical complications. Prevention of recurrence of IPA has occurred in most reported series [5, 10, 11, 24, 27, 32–34]. However, in a study on 37 resections with a more detailed report on post-operative complications [9], 18 had an uneventful post-operative course, including one patient who had emergency surgery for

Table 4. Prognostic factors in surgery for invasive pulmonary aspergillosis

Morbidity and age
Prognosis of the underlying disease
Presence of lung disease, lung function
Limited resection
Well-trained surgeon
Additional treatments (antifungal, nutrition, exercise training, psychological and social support)
Multidisciplinary teamwork

haemoptysis; three had post-operative haemorrhage; one required a repeat thoracotomy; and one wound and one nonfungal chest infection were seen. Two patients underwent revision pneumonectomy after initial lobectomy for progressive *Aspergillus* infection; of these, one died soon afterwards and the other is a long-term survivor. Two patients died of *Aspergillus* pneumonia, 3 and 8 days after surgery; another died of disseminated aspergillosis 18 days post-operatively; three further patients died of respiratory failure at 1–10 days; and another died of septic shock 4 days after surgery. All of these early deaths were presumed to be due to progression of IPA. Two patients died of interstitial pneumonitis after allogeneic bone marrow transplant, 27 and 52 days after surgery; although radiologically not typical, IPA cannot be excluded [9]. The peri- and post-operative surgical risks are summarised in table 3 [8].

Prognostic factors and outcome

Successful therapy of the underlying disease is the strongest prognostic factor for IPA, such as the complete remission of the haematological disease. After surgery for IPA, the survival of patients is limited due to relapse of uncontrolled malignancy but not due to the complications of the surgical procedure [8, 10, 29, 34]; in series with a high rate of post-operative progression of IPA, the antifungal management and an intense monitoring of IPA has to be re-evaluated [9]. In a retrospective analysis of 54 patients with localised IPA, survival at 6 months was 70% in surgically and 42% in medically treated patients. In general, medically treated patients have a worse World Health Organization performance score than the surgical patients, in whom the duration of neutropenia is longer [35]. Resection can eliminate IPA if the lesions can be resected completely in a single or multiple operations. In summary, the outcome of surgery for IPA depends on several factors (table 4). It is important that surgery has to be complemented by various other treatments [2].

Conclusions

The conservative approach by an early adequate antifungal therapy is of utmost importance. A high index of suspicion is necessary for early diagnosis of IPA. In an interdisciplinary setting the indication for surgery should be deliberately discussed. Massive haemoptysis requires emergency surgery, whereby pneumonectomy should be avoided whenever possible. Lesions near to great vessels should be considered for resection. Parenchyma-saving surgical procedures are preferred techniques in selected patients with clinical and radiological signs of localised IPA early in the course, when antifungal therapy has failed and prior to subsequent immunosuppressive therapy or chemotherapy. In thoroughly selected patients, prognosis of IPA is mostly determined by the underlying disease.

Statement of Interest

O.A. Cornely is supported by the German Federal Ministry of Education and Research (BMBF; grant 01KN1106) and has received research grants from, is an advisor to, or received lecture honoraria from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist, F2G, Genzyme, Gilead, GSK, Merck/MSD, Miltenyi, Optimer, Pfizer, Quintiles, Sanofi Pasteur and Viropharma.

References

1. Walsh TJ, Anaissie EJ, Denning DW, *et al.* Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46: 327–360.
2. Massard G, Olland A, Santelmo N, *et al.* Surgical management of thoracic aspergillosis. *In*: Rohde G, Subotic D, eds. Complex Pleuropulmonary Infections. *Eur Respir Monogr* 2013; 61: 50–57.
3. Bassetti M, Righi E. Fungal pulmonary infections: the conservative approach. *In*: Rohde G, Subotic D, eds. Complex Pleuropulmonary Infections. *Eur Respir Monogr* 2013; 61: 37–49.
4. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2007; 30: 782–800.

5. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev* 2011; 20: 156–174.
6. Alexander B, Pfaller M. Contemporary tools for the diagnosis and management of invasive mycoses. *Clin Infect Dis* 2006; 43: S15–S27.
7. Hage CA, Knox KS, Davis TE, *et al.* Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. *Curr Opin Pulm Med* 2011; 17: 167–171.
8. Reichenberger F, Habicht JM, Gratwohl A, *et al.* Diagnosis and treatment of invasive aspergillosis in neutropenic patients. *Eur Respir J* 2002; 19: 743–755.
9. Yeghen T, Kibbler CC, Prentice HG, *et al.* Management of invasive pulmonary aspergillosis in hematologic patients: A review of 87 consecutive cases at a single institution. *Clin Infect Dis* 2000; 31: 859–868.
10. Reichenberger F, Habicht JM, Kaim A, *et al.* Lung resection for invasive pulmonary aspergillosis in neutropenic patients with hematologic diseases. *Am J Respir Crit Care Med* 1998; 158: 885–890.
11. Baron O, Guillaumé B, Moreau P, *et al.* Aggressive surgical management in localized pulmonary mycotic and nonmycotic infections for neutropenic patients with acute leukemia: report of eighteen cases. *J Thorac Cardiovasc Surg* 1998; 115: 63–69.
12. Kramer MR, Denning DW, Marshall SE, *et al.* Ulcerative tracheobronchitis after lung transplantation. A new form of invasive aspergillosis. *Am Rev Respir Dis* 1991; 144: 552–556.
13. Kessler R, Massard G, Warter A, *et al.* Bronchial-pulmonary artery fistula after unilateral lung transplantation: a case report. *J Heart Lung Transplant* 1997; 16: 674–677.
14. Herbrecht R, Denning DW, Patterson T, *et al.* Voriconazole *versus* amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002; 347: 408–415.
15. Cornely OA, Maertens J, Bresnik M, *et al.* Liposomal amphotericin B as initial therapy for invasive mould infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad Trial). *Clin infect Dis* 2007; 44: 1289–1297.
16. Martino R, Parody R, Fukuda T, *et al.* Impact of the intensity of the pretransplantation conditioning regimens in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Blood* 2006; 108: 2928–2936.
17. Wong K, Waters CM, Walesby RK. Surgical management of invasive pulmonary aspergillosis in immunocompromised patients. *Eur J Cardiothorac Surg* 1992; 6: 138–143.
18. Robinson LA, Reed EC, Galbraith TA, *et al.* Pulmonary resection for invasive *Aspergillus* infections in immunocompromised patients. *J Thorac Cardiovasc Surg* 1995; 109: 1182–1196.
19. Caillot D, Casasnovas O, Bernard A, *et al.* Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol* 1997; 15: 139–147.
20. Habicht JM, Gratwohl A, Tamm M, *et al.* Diagnostic and therapeutic thoracic surgery in leukemia and severe aplastic anemia. *J Thorac Cardiovasc Surg* 1997; 113: 982–988.
21. Lupinetti FM, Behrendt DM, Giller RH, *et al.* Pulmonary resection for fungal infection in children undergoing bone marrow transplantation. *J Thorac Cardiovasc Surg* 1992; 104: 684–687.
22. Massard G, Lioure B, Wihlm GM, *et al.* Resection of mycotic lung sequestra after invasive aspergillosis. *Ann Thorac Surg* 1993; 55: 563–564.
23. Bernard A, Caillot D, Couailler JF, *et al.* Surgical management of pulmonary aspergillosis in neutropenic patients. *Ann Thorac Surg* 1997; 64: 1441–1447.
24. Habicht JM, Reichenberger F, Gratwohl A, *et al.* Surgical aspects of resection for suspected invasive pulmonary fungal infection in neutropenic patients. *Ann Thorac Surg* 1999; 68: 321–325.
25. Massard G. Place de la chirurgie dans le traitement des aspergilloses thoraciques. [Role of surgery in the treatment of pulmonary aspergillosis]. *Rev Mal Respir* 2005; 22: 466–472.
26. Young VK, Hassan AM, Luke DA, *et al.* Operation for cavitating invasive pulmonary aspergillosis in immunocompromised patients. *Ann Thorac Surg* 1992; 53: 621–624.
27. Moreau P, Zahar JR, Milpied N, *et al.* Localized invasive pulmonary aspergillosis in patients with neutropenia. Effectiveness of surgical resection. *Cancer* 1993; 72: 3223–3226.
28. Salerno CT, Ouyang DW, Pederson TS, *et al.* Surgical therapy for pulmonary aspergillosis in immunocompromised patients. *Ann Thorac Surg* 1998; 65: 1415–1419.
29. Gow KW, Hayes-Jordan AA, Billups CA, *et al.* Benefit of surgical resection of invasive pulmonary aspergillosis in pediatric patients undergoing treatment for malignancies and immunodeficiency syndromes. *J Pediatr Surg* 2003; 38: 1354–1360.
30. Habicht JM, Passweg J, Kuhne T, *et al.* Successful local excision and long-term survival for invasive pulmonary aspgergillosis during neutropenia after bone marrow transplantation. *J Thorac Cardiovasc Surg* 2000; 119: 1286–1287.
31. Massard G, Dabbah A, Wihlm JM, *et al.* Pneumonectomy for chronic infection is a high-risk procedure. *Ann Thorac Surg* 1996; 62: 1033–1038.
32. Caillot D, Mannone L, Cusienier B, *et al.* Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. *Clin Microbiol Infect* 2001; 7: Suppl. 2, 54–61.

33. Pidhorecky I, Urschel J, Anderson T. Resection of invasive pulmonary aspergillosis in immunocompromised patients. *Ann Surg Oncol* 2000; 7: 312–317.
34. Matt P, Bernet F, Habicht J, *et al.* Predicting outcome after lung resection for invasive pulmonary aspergillosis in patients with neutropenia. *Chest* 2004; 126: 1783–1788.
35. Habicht JM, Matt P, Passweg JR, *et al.* Invasive pulmonary fungal infection in hematological patients: is resection effective? *Hematol J* 2001; 2: 250–256.

Chapter 7

Actinomycosis of the lung and pleura

Martin Kolditz[*] *and Adelheid End*[#]

SUMMARY: Pulmonary actinomycosis is a rare and slowly progressing bacterial lung infection. Actinomyces are commensal bacteria of the oropharynx. Risk factors for pulmonary infection include aspiration and poor dental hygiene; it is not necessarily associated with an immunosuppressed state. Radiological and clinical appearances are nonspecific and mimic a variety of other lung diseases including cancer. Diagnosis requires microbiological isolation of the bacteria from an infected specimen or histopathological evidence of sulfur granules, usually obtained after bronchoscopic, transthoracic or surgical biopsy. Long-term and high-dose antibiotic treatment is essential to achieve high clinical cure rates and good prognosis. Penicillin remains the drug of choice; doxycycline, macrolides and clindamycin have been used successfully as alternatives. Duration of antibiotic treatment should be individualised according to the resolution of symptoms and radiological lesions. Surgical treatment is reserved for patients developing complications, such as massive haemoptysis or empyema, and for those in whom a medical diagnosis cannot be established.

[*]Dept of Pulmonology, Medical Clinic I, University Hospital Carl Gustav Carus, Dresden, Germany.
[#]Dept of Thoracic Surgery, Medical University of Vienna, Vienna, Austria.

Correspondence: M. Kolditz, Dept of Pulmonology, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany.
Email: martin.kolditz@uniklinikum-dresden.de

Eur Respir Monogr 2013; 61: 66–80.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10040912
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Actinomycosis is a rare and slowly progressive infectious disease that can affect a variety of organ systems including the lung. It is caused by filamentous Gram-positive anaerobic bacteria of the genus Actinomyces. The chronic and granulomatous nature of this infection frequently causes diagnostic problems, as the clinical and radiological appearance mimics a variety of other lung diseases, such as neoplastic disease, tuberculosis, pneumonia and pulmonary abscesses. Additionally, actinomycosis can cause complicated pleuropulmonary infections and affect endobronchial structures and the chest wall, leading to cutaneous fistulae, empyema or bronchial obstruction. Even for experienced physicians, the diagnosis is challenging and frequently established only after several months of symptom duration. Surgical procedures often are employed for diagnostic confirmation and differentiation from other lung diseases. However, once diagnosed, the prognosis of pulmonary actinomycosis is generally good, as specific and prolonged antibiotic treatment can lead to complete recovery. Thus, in order to enable timely treatment and to avoid unneeded and potentially dangerous interventions, a dedicated diagnostic approach is necessary. As clinical experience in individual centres is sparse because of the low incidence of this disease, continuous vigilance and spread of knowledge about this infection is required, which is the main focus of this chapter.

Epidemiology

Epidemiological data of actinomycosis are unreliable, as a significant number of missed or misclassified cases has to be assumed. The incidence reported in recent reviews is around 1:300 000 [1–4]. This assumption is based on historical data from a US case series showing one case for every 59 000 hospital admissions during 1973–1982 [5], which had declined by >50% in comparison with an earlier US series from 1935–1970 [6]. According to German reference laboratory data, the incidence of cervicofacial actinomycosis was estimated to be as high as one in 40 000 inhabitants [7]. The most recent data arise from an Icelandic population-based study, where an annual incidence of approximately one in 100 000 inhabitants during 1984–2007 (66 cases) was reported [8]. It is thought that the disease frequency has decreased during the last decades due to improved oral hygiene and the widespread use of antibiotic treatment. However, because of diagnostic difficulties and the fastidious nature of the organism for microbiological isolation, the true incidence is probably higher.

Actinomycosis can affect patients of any age, but, according to historical case series, epidemiology peaks during the middle-age decades, and males are three times more frequently infected than females [6, 9]. This male- and middle-age predominance has been confirmed by recent case series for pulmonary infections [10–17].

The pulmonary form of actinomycosis constitutes ~15–20% of the total burden of the disease [1, 4, 6], although higher [5, 9, 18] and lower [7, 8] estimates have been reported. The majority of cases present as cervicofacial infection [6–8]; another 20% of cases accounts for abdominal infections. Other sites, such as cutaneous, genito-urinary and central nervous system infections also can occur.

Microbiology and histopathology

Actinomycetes are part of the normal flora of the human oropharynx, and the gastrointestinal and urogenital tract [19]. Molecular genotyping techniques have led to an increased number of actinomyces species causing human infection being identified during recent years [19]. Today >40 species are known, of whom *Actinomyces israelii* is the most common pathogen [3]. Less frequent agents of human infection include *Actinomyces naeslundii*, *Actinomyces odontolyticus*, *Actinomyces viscosus*, *Actinomyces meyeri* and *Actinomyces gerencseriae* [3]. Humans are the only known reservoir for these disease-causing species, but no person-to-person transmission has been documented yet [3, 20].

Actinomycetes are fastidious bacteria and difficult to culture. They are slow growing and usually cultured on selective agar medium at 37°C under strict anaerobic conditions for up to 3 weeks [3, 4]. In everyday clinical practice, bacterial confirmation of a pathologically diagnosed pulmonary actinomycosis is obtained in only a minority of cases. In the two most recent large series of thoracic actinomycosis, culture confirmation of the infection was shown in <10% [16, 17]. Reasons for this low culture yield include frequent previous antibiotic therapy, bacterial overgrowth of more rapidly growing co-isolates and inadequate culturing techniques. As actinomycetes are sensitive to most antibiotics commonly used in out- and inpatients, even a short course of antibiotic pre-treatment might inhibit their growth in culture [21–23]. Thus, if actinomycosis is suspected, adequate specimen sampling should be performed before empirical antibiotic treatment is begun. The clinical laboratory must be alerted and the specimen sent as quickly as possible and under anaerobic conditions. As actinomycetes are members of the normal oropharyngeal flora, isolation from primary unsterile materials, such as sputum, may represent colonisation and not infection. More appropriate clinical specimens include samples of pus or lung tissue, especially if they contain sulfur granules. To establish a more rapid suspicion of actinomycosis, a gram stain demonstrating branching, Gram-positive and filamentous bacilli can be used.

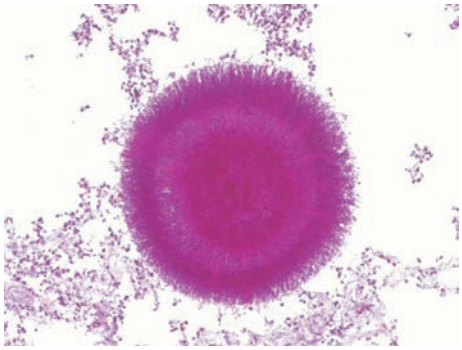


Figure 1. Low magnification showing a typical sulfur granule with filamentous amphophilic, branching bacteria in the centre and radially oriented filaments covered with deeply eosinophilic material at the periphery.

In the future, molecular methods, such as PCR, 16s rRNA sequencing and mass spectrometry will allow more rapid and accurate microbiological confirmation of the disease [19, 24–26]. However, with growing employment of these sensitive techniques, adequate clinical specimen sampling to exclude possible contamination by colonising bacteria becomes even more relevant. To date, clinical data on molecular techniques are still sparse, and further study to prove their sensitivity and specificity for clinical decision making are warranted.

Given these problems associated with microbiological confirmation of the infection, histological examination of obtained tissue is especially important for diagnosis. The presence of so called sulfur granules is strongly supportive of actinomycosis. Sulfur granules are colonies of organisms that appear as round or oval basophilic masses with radiating eosinophilic terminal clubs on staining with haematoxylin–eosin (fig. 1) [9]. The numerous granules containing actinomycetes can best be seen with the Gomori methenamine silver and the Brown and Brenn stains [4, 9, 18]. Although the number of sulfur granules in infected tissue can be low and, in a minority of culture-confirmed cases, even absent [9], their presence in lung tissue of a patient with suspected actinomycosis is considered highly supportive for this infection [16, 17]. In fact, the histologically confirmed presence of sulfur granules has been used as main diagnostic criterion in all larger published case series of pulmonary actinomycosis during the last decades. However, specificity of sulfur granules for actinomycosis is not 100%, as they can occasionally occur in nocardiosis and fungal infections [18].

Actinomycetes are commonly isolated together with other bacteria, which potentially causes confusion or diagnostic errors. Aerobically growing Gram-positive and Gram-negative species, as well as anaerobically growing species, often commensals of the oropharynx, have been described, but data originate mainly from cervicofacial actinomycosis [27]. In the current author's series of 49 pulmonary infections [16], co-pathogens were isolated in 47% of cases, with a predominance of Gram-negative enterobacteria (unpublished data). The clinical relevance of these co-pathogens has not been established, but given the good results of small-spectrum penicillin treatment in pulmonary actinomycosis, specific treatment is probably not needed in many cases [6, 16, 18]. Conversely, a possible contribution to the pathogenicity of actinomycetes by mixed infections, *e.g.* by creating a more anaerobic environment, has been discussed [9, 18].

Clinical management

Clinical data on the management of pulmonary actinomycosis are sparse and no randomised controlled studies exist. Evidence thus is limited to retrospective case series. All identified series describing >10 patients published between 1990 and 2012 are summarised in table 1. The largest case number was 49 patients. Series focusing primarily on radiological features were excluded [28, 29].

Clinical risk factors

Pulmonary actinomycosis is thought to result predominantly from aspiration of oropharyngeal secretions containing actinomycetes, but can sometimes also occur after oesophageal perforation, local spread from cervicofacial infection or haematogenous spread [18]. Thus, established risk factors for pulmonary infection include poor oropharyngeal or dental hygiene, as well as risk factors for aspiration syndromes, such as alcoholism [16, 18]. As actinomycetes preferentially grow

Table 1. Case series of pulmonary actinomycosis published between 1990 and 2012 with >10 patients

First author [ref.]	Year of publication	Country	Cases	Cases with surgery involved
Kinnear [10]	1990	UK	19	12 (63)
Hsieh [11]	1993	Taiwan	17	9 (53)
Rizzi [12]	1996	Italy	13	12 (92)
Dujneungkunakorn [13]	1999	Thailand	16	10 (63)
Baik [30]	1999	Korea	25	14 (56)
Endo [14]	2002	Japan	13	13 (100)
Lu [15]	2003	Taiwan	14	14 (100)
Choi [31]	2005	Korea	28	13 (46)
Kolditz [16]	2009	Germany	49	3 (6)
Song [17]	2010	Korea	40	17 (43)

Data are presented as n or n (%).

under anaerobic conditions, the presence of devitalised lung tissue caused by underlying chronic lung disease is another risk factor [9, 16–18].

Current data on dental status in thoracic actinomycosis are sparse. In three recent series, poor dental status or oral hygiene was documented in 27–77% of cases [12, 14, 16]. Alcoholism was confirmed in three recent series as risk factor with frequencies of 23–38% [12, 14, 16]. The higher incidence of pulmonary actinomycosis in patients with underlying lung diseases is also supported by recent series, where pre-existing pulmonary comorbidity was documented in 20–69% of cases [12, 14, 16, 17, 30, 31], mainly consisting of chronic obstructive pulmonary disease, bronchiectasis, chronic mycobacterial disease and aspergilloma. Accordingly, a high frequency of 61–70% of current or former smokers has been described [14, 16, 17, 31]. In some publications, there was an elevated number of patients with coexisting diabetes mellitus [13, 14, 31]. However, in all recent series reporting comorbidities, a significant proportion of nearly 50% of patients without any relevant underlying disease was noted, indicating that thoracic actinomycosis is not confined to multimorbid patients [14, 16, 30, 31].

In three case series, antibiotic pre-treatment was documented at rates of between 45% and 69% [10, 14, 16]. In the current author's series [16], 50% of the patients with ineffective antibiotic treatment prior to hospitalisation had received a quinolone, an antibiotic considered ineffective for actinomyces treatment [21]. This clinical information might also raise suspicion for the presence of rare pathogens, such as actinomycetes.

The influence of specific components of the immune response on actinomycosis and, thus, the clinical relevance of concurrent immunosuppressive diseases or medications on incidence and outcome remain unclear [4]. An elevated incidence in immunocompromised patients, such as those with HIV or on chronic steroid therapy, cancer chemotherapy or immunosuppressive therapy after transplantation has not been reported [1, 4, 9, 32]. Accordingly, the proportion of severely immunocompromised patients in all recent case series of pulmonary actinomycosis was either remarkably low or absent. For most immunosuppressive conditions, evidence for actinomyces infection only derives from case reports [32]. In HIV-infected patients, the prevalence of actinomycosis has remained low and pulmonary infections rarely occur [33–36]. Pulmonary actinomycosis also has been described in case reports of patients with acute leukaemia and non-Hodgkin's lymphoma [37–39], and there has been a recent series of 10 patients with chronic granulomatous disease and actinomyces infection; two of these patients were children with pulmonary disease with a complicated course [40]. For treatment-related immunosuppression, again only a few cases of pulmonary actinomycosis have been reported, *e.g.* with steroid treatment for systemic lupus erythematodes [41], steroid treatment combined with methotrexate for rheumatoid arthritis [42], cyclophosphamide treatment for cryoglobulinemia [16], infliximab treatment for Crohn's disease [43] or systemic sclerosis [44], and immunosuppression after solid

Table 2. Clinical symptoms in patients with pulmonary actinomycosis from recent case series (excluding series reporting exclusively on surgical cases)

	Kinnear [10]	Hsieh [11]	Rizzi [12]	Dujneungkunakorn [13]	Baik [30]	Choi [31]	Kolditz [16]	Song [17]	Summary
Subjects n	19	17	13	16	25	28	49	40	
Symptom frequency %									
Cough	84	47	8	100	68	86	71	55	67
Sputum	74	6	NG	NG	60	86	55	45	56
Haemoptysis	32	53	46	62	72	79	12	60	49
Chest pain	68	35	38	NG	44	11	41	18	34
Weight loss	52	NG	NG	25	16	21	37	NG	31
Fever	21	18	54	31	32	7	37	15	26
Night sweats	32	NG	NG	NG	NG	NG	25	NG	26
Dyspnoea	47	6	NG	NG	NG	NG	14	NG	20
Swelling of chest wall	11	6	NG	NG	NG	NG	8	NG	8
Median symptom duration prior to diagnosis in months	NG	1	NG	9	2–3	2.5	2	3	

NG: not given.

organ transplantation [45, 46]. Taken together, it can be concluded from these data that, although actinomycosis can occur in severely immunosuppressed patients, its prevalence in this setting remains very low and severe immunosuppression is certainly not a precondition for pulmonary actinomycosis.

Clinical symptoms

Symptoms of pulmonary actinomycosis are nonspecific and consist of a variety of pulmonary and systemic complaints, which often mimic features of tumour disease or tuberculosis. In recent series, predominant symptoms included cough, productive sputum, haemoptysis, chest pain, weight loss and fever [16, 17]. In surgical case series, haemoptysis was the leading complaint [14, 15]. Asymptomatic patients detected at routine investigations are rarely affected. The infection can extend across anatomical barriers, causing chest wall or mediastinal involvement or empyema. Endobronchial manifestations can cause airway obstruction or broncholithiasis.

Given the chronic nature of this infection, the nonspecific presentation and the regular suspicion of alternative lung diseases at first presentation, symptom duration prior to diagnosis in recent case series lasted up to 60 months, with a median duration of several months.

An overview of presenting complaints in recent case series of pulmonary actinomycosis (series reporting exclusively on surgical cases are excluded) is given in table 2.

Laboratory tests

No specific laboratory marker of actinomycosis exists. Routine parameters reflecting the chronic inflammatory character of the disease are often pathological. In one recent series of 49 patients, a raised erythrocyte sedimentation rate was noted in 80%, leukocytosis in 60% and elevated C-reactive protein values in 72% [16].

Radiological appearance

The predominant findings on chest radiograph are pulmonary masses or infiltrates, which are described in >80% of cases [10, 13–17, 30, 31].

One-sided appearance is usual, but bilateral or even disseminated lung involvement can occur. Many [5, 11, 12, 14, 17], but not all [10], series report on a right sided predominance of the lesions, which has been linked to the aspiration pathophysiology of pulmonary actinomycosis. Abscesses or cavitary lesions can be seen. Less frequently, pleural effusion, atelectasis or bronchiectasis is found as the only radiological abnormality. Examples of plain radiographs from patients with pulmonary actinomycosis are shown in figure 2.

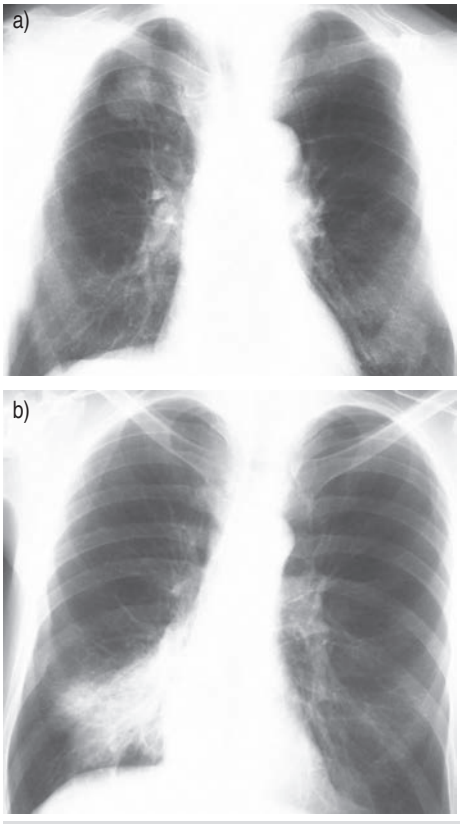


Figure 2. Examples of plain radiographs from patients with confirmed pulmonary actinomycosis presenting with a) a tumour-like mass in the right upper lobe and b) an infiltrate in the right lower lobe.

As neoplastic disease has to be considered in many cases, and additional imaging usually is warranted. Chronic actinomyces infections infiltrate across anatomical barriers and, therefore, actinomycosis may spread from the lungs to the pleura, mediastinum and chest wall. A chest computed tomography (CT) scan should be performed for better differentiation and planning of invasive diagnostic procedures [29, 47]. On CT scans, areas of necrotic low attenuation within the consolidations could be detected in up to 75% [17, 28, 29], and mediastinal lymph node enlargements have been described in up to 50% [17, 28, 31]. Endobronchial manifestations, including broncholiths, were seen in up to 35% [17, 31]. Rare but important complications, such as pericardial involvement or foreign bodies, can be detected [29, 48–50]. Examples of chest CT scans from patients with pulmonary actinomycosis are shown in figure 3.

Few data exist of magnetic resonance imaging of thoracic actinomycosis [51]. A role in the differentiation of chest wall involvement and spreading of peri- or myocardial, as well as vertebral, infection is suggested.

If a positron emission tomography is performed because of the suspicion of lung cancer, pulmonary actinomycosis lesions may show enhanced 2-fluoro-2-deoxy-D-glucose uptake, thus not allowing further differentiation from neoplastic disease [52, 53].

Diagnosis

Given the nonspecific clinical and radiological presentation of patients with pulmonary actinomycosis, the infection is clinically rarely presumed at presentation. Most frequently, initial suspected diagnoses are malignancy, pneumonia and tuberculosis (table 3).

Thus for confirmation of the infection, as well as differentiation from other lung diseases, invasive procedures to obtain adequate specimen for microbiological and histological analysis are required. Cultural confirmation always should be intended, but given the discussed problems with empirical antimicrobial pre-treatment, overgrowth of associated bacteria and the fastidious nature of actinomycetes, cultural results will be negative in the majority of cases. Further diagnostic confusion can be caused by the detection of actinomycetes in sputum or bronchial secretions from patients with pulmonary comorbidities or lung cancer, which in many cases might reflect colonisation of necrotised lung tissue rather than infection [54]. Thus, primarily sterile specimens, such as lung tissue biopsies, obtained by procedures that minimise contamination risk should be intended. This becomes even more evident if new molecular diagnostic methods, such as PCR with

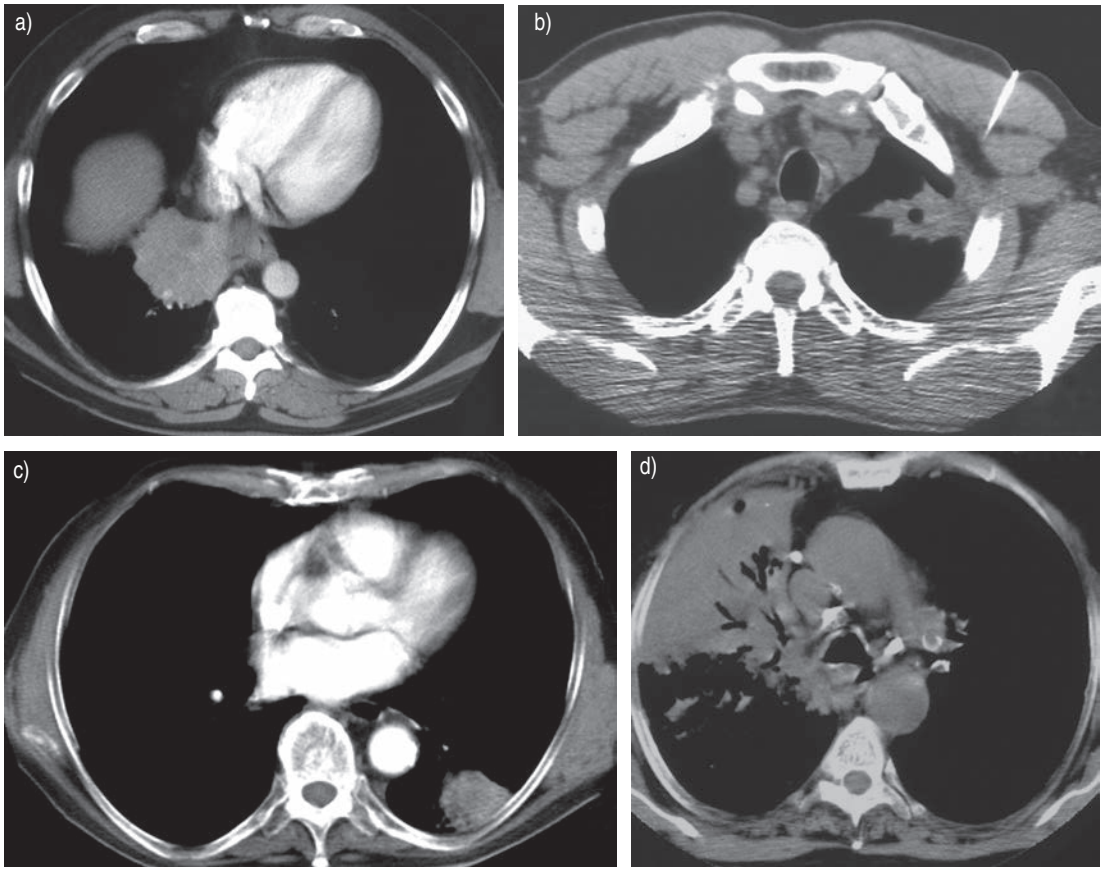


Figure 3. Examples of chest computed tomography (CT) scans from patients with confirmed pulmonary actinomycosis presenting with a) a central pulmonary mass in the right lower lobe, b) a localised abscessing infiltrate in the left upper lobe during CT-guided transthoracic needle biopsy, c) a peripheral mass in the left lower lobe and d) a diffuse infiltrate in the right upper lobe.

16S rRNA gene sequencing and mass spectrometry, become available for bacterial confirmation in routine clinical practice [19, 24–26]. Conversely, as these techniques allow more accurate and timely actinomyces detection, microbiological confirmation could be improved considerably. Today these techniques are still available only in specialised laboratories.

Meanwhile, diagnostic confirmation in everyday practice, in most cases, is obtained by the typical histological picture, including the demonstration of sulfur granules in infected tissue [9]. Thus, suspicion of thoracic actinomycosis and consideration of the most important differential

Table 3. Suspected clinical diagnoses prior to thoracic actinomycosis confirmation in recent case series with available data

	Hsieh [11]	Rizzi [12]	Baik [30]	Endo [14]	Kolditz [16]	Song [17]
Subjects n	17	13	25	13	49	40
Suspected diagnosis %						
Malignancy	59	38	44	23	49	45
Mycobacterial infection		15	24	15	14	18
Pneumonia/abscess	29		16	54	14	5
Actinomycosis				8	2	18
Bronchiectasis		15	8		4	
Aspergilloma		8				7
Other	12	23	8		16	

diagnoses followed by carefully planned specimen sampling are central diagnostic steps. Material should be sent as quickly as possible and under anaerobic conditions for microbiological investigations, and both the microbiologist and the cytopathologist should be informed about the suspected diagnosis.

The frequent suspicion of pulmonary malignancy in case series often lead to diagnostic surgical procedures. In publications from the 1990s, the indication for diagnostic surgery after exclusion of patients with emergency symptoms, such as fulminant haemoptysis, varied between 37% and 85% [10–12, 14, 30, 31]. However, with the broad availability of less invasive options, such as image-guided transthoracic puncture or bronchoscopic techniques, the frequency of surgical procedures for diagnostic confirmation declined to 2–15% in many recently published series [16, 17]. As adequate antibiotic treatment is associated with a good prognosis, even in complicated cases, a diagnostic strategy that avoids surgery might prevent considerable morbidity, discomfort, costs and diagnostic delay.

For pleural or chest wall infections, specimens can be obtained by puncture or small biopsies. Endobronchial lesions easily can be examined by bronchoscopy. For lung infection, different techniques have been employed. With peripheral lesions, transthoracic needle biopsy by ultrasound or CT guidance would be a preferred procedure. In the two most recent publications, this technique was successfully used in 25% of patients [16, 17]. Additionally, a variety of bronchoscopic techniques have been performed, including endobronchial biopsy, radiologically guided transbronchial biopsy by catheter aspiration or forceps and transbronchial needle aspiration. In the series by KOLDITZ *et al.* [16], bronchoscopic biopsy lead to the diagnostic detection of sulfur granules in 32 (65%) of 49 patients; however, in ~30% of these patients, more than one procedure had to be performed. Of the 47 patients without an indication for therapeutic surgery, in 46 (98%) cases, the diagnostic confirmation was obtained by nonsurgical methods. This contradicts previous statements that bronchoscopy might be an ineffective diagnostic approach in pulmonary actinomycosis [18]. According to the present authors' view, in the absence of therapeutically indicated surgery, a diagnostic approach involving either one or repeated diagnostic attempts by bronchoscopy and/or transthoracic needle aspiration for microbiological or histological confirmation and to make alternative diagnoses less likely is the recommended algorithm before a surgical diagnostic approach should be considered.

Even after diagnostic confirmation, the differentiation of actinomycosis from cancer can remain problematic, as coexistence of both, albeit uncommon, has been described [13, 17, 55]. Thus, the final diagnosis of pulmonary actinomycosis requires the combination of possible risk factors, a compatible clinical and radiological presentation, the detection of sulfur granules in infected tissue, ideally supplemented by microbiological confirmation from culture or by molecular methods in appropriate tissue specimen, and a favourable response to antibiotic treatment.

Clinical complications

Due to the common use of empirical antibiotic treatment, the improved access to healthcare facilities and the broad availability of diagnostic methods, the rate of patients presenting very late with complicated disease presentations has declined from what is was decades ago, where large, bulky lesions and complications, such as chest wall involvement, abscess formation and pleural empyema, could regularly be seen [16, 17]. However, because of the slowly progressive and chronic ongoing infection caused by actinomycetes, their nonspecific clinical and radiological appearance and their ability to spread beyond anatomical borders, diagnostic delays leading to advanced disease states still occur.

The most frequently reported clinical complication is haemoptysis, which occurred in ~50% of patients from recent series and can progress to life-threatening major haemoptysis resulting in emergency interventions. In one series of 14 patients presenting for surgery with haemoptysis due to actinomycosis, 50% presented with severe bleeding with blood losses exceeding 200 mL [15]. Catheter-guided embolisation had been performed in seven cases prior to surgery without success

[15]. Other series of surgically treated patients reported major or recurrent haemoptysis as an indication for therapeutic surgery, with a similar incidence of 50% [12, 14, 17]. However, a large number of nonmajor haemoptysis can be treated medically with good success [16, 56].

Another complication potentially requiring surgical intervention is the presence of pleural empyema. Whereas the occurrence of pleural effusions has been described in up to 21% of cases in a recent series [31], many of these effusions would probably not fulfil the criteria of purulent or complicated parapneumonic effusions. Successful medical treatment of patients with pulmonary actinomycosis complicated by pleural effusion or ''empyema'' has been described [11, 57]. Clinical data allowing for specific management recommendations of actinomycosis-related pleural effusions are absent. Thus, a concept in analogy to the procedures recommended for patients with parapneumonic pleural effusions is suggested. Here, medical treatment is indicated for very small and uncomplicated effusions with careful follow-up by imaging studies [58, 59]. In contrast, the presence of purulent fluid or of a complicated pleural effusion, defined as loculated presentation, evidence of bacteria or pH of <7.2 in pleural fluid after diagnostic thoracentesis results in the need for rapid evacuation by means of surgery or pleural tube insertion [58, 59].

Endobronchial actinomyces infection, either isolated or within a pulmonary infection, can cause relevant airway obstruction [60]. In bronchoscopy, it presents as necrotic, whitish or yellowish endobronchial mass or irregular granular thickening. In one series, the bronchoscopic finding of airway narrowing has been described in nine out of 16 cases [13]. Endobronchial actinomycosis can be associated with either broncholiths [48, 61] or foreign bodies [49, 62, 63]. The presence of broncholiths has been detected in up to 34% of cases after CT imaging [31]. They consist of endobronchial calcified material, which is often formed by erosion of calcified lymph nodes into the airway as a result of a granulomatous process [47, 48]. They can cause relevant airway narrowing or even complete bronchial obstruction, and are associated most frequently with a history of tuberculosis or the aspiration of foreign bodies [47, 48]. The chronic granulomatous inflammation associated with actinomycosis might cause broncholithiasis by itself [61], although it has been suggested that most cases were associated with pre-existing broncholithiasis and secondary infection by actinomycetes [48]. In the absence of a foreign body, the majority of endobronchial actinomycoses can be cured with antibiotics [13], but, in some cases, bronchoscopic treatment of airway obstruction, broncholith removal [17, 60] or even surgery [61] might be indicated. Singular cases also have been reported with endotracheal [64] or vocal cord [65] infection by actinomycetes.

A variety of other complications resulting from local spread of actinomycosis from the lungs across anatomical barriers has been described in case reports. Chest wall swelling was reported in up to 10% of recent series [10, 16], but chest wall fistulae or rib destruction have been found only rarely [16, 17]. Local mediastinal invasion of actinomycosis can cause peri- and myocardial infection with either pericardial effusion [50, 66–68] or obstruction of central veins, which even might progress to superior vena cava syndrome [50, 69]. Transphrenic spread can lead to intra-abdominal infection [70], and local invasion into the pulmonary circulation has caused pulmonary artery aneurysm [71] or systemic-to-pulmonary artery fistula [72]. Occasionally, bacteraemia of actinomyces associated with pulmonary disease has been reported [36, 73, 74]. Most of these complications require individual multidisciplinary treatment decisions, but, for all cases, timely adequately dosed and prolonged treatment with antibiotics presents the mainstay of treatment.

Treatment and prognosis

Once the diagnosis of pulmonary actinomycosis has been established, the prognosis of this infection is generally good, as antibiotic treatment often leads to complete recovery. The therapeutic principle of actinomycosis consists of the prolonged administration of adequately selected and dosed antibacterial substances [1, 18, 20], and primary surgical interventions should be reserved for patients presenting with specific complications. Additional management strategies

follow the established recommendations from guidelines for pneumonia [75], sepsis [76] or pleural effusion [58] management, where appropriate. Treatment should be complemented by measures to improve existing risk factors, such as restoration of a poor dental status, improvement of oropharyngeal hygiene, management of aspiration syndromes or therapy of impaired immune function, as it seems plausible that these may diminish the risk of relapses or re-infection.

Antibiotic treatment

Substances

Antibiotics with *in vitro* activity against actinomycetes include penicillins, cephalosporins, carbapenems, tetracyclins, macrolides and clindamycin, whereas quinolones are considered inappropriate [21–23]. Treatment recommendations derive from clinical experience only, as randomised trials have not been performed. If actinomycosis is left untreated, the prognosis is ultimately fatal, but with adequate antibiotic therapy over a prolonged period, complications can be prevented and the infection cured in most cases.

Three recent papers reporting on antibiotic susceptibility testing for clinical actinomyces isolates showed an excellent overall susceptibility to most β-lactams (including benzylpenicillin, amoxicillin, ceftriaxone, meropenem and piperacillin), doxycycline, clindamycin and macrolides, as well as some newer antibiotics like linezolid and tigecycline [21–23]. However, different actinomyces species showed relevant resistance differences to some antibiotics, indicating that species identification might be important [22]. Moreover, many strains were resistant to quinolones, vancomycin, aztreonam and amikacin, which are therefore not considered adequate treatment options [21–23].

The suggested primary treatment consists of intravenous penicillin over 2–6 weeks followed by a prolonged period of oral penicillin [1, 18]. This recommendation derives from early case series, where success rates of 90% with penicillin have been reported [6]. However, surgical debulking was involved in >50% of these cases, mostly for diagnostic reasons [6]. Penicillin remains the drug of choice to date, based on the broad experience from published case series [4, 11, 12, 16, 17] and the documented sensitivity of essentially all tested actinomyces isolates [21–23]. In general, 20–30 million units of penicillin per day are given for the first 2–6 weeks followed by oral therapy with penicillin V [18]. Alternatively, ampicillin and amoxicillin with or without clavulanic acid have been used successfully in case series [17, 30, 31]. Allergy against penicillin is an important limitation, which caused an antibiotic switch in up to 37% of patients [16]. Here, doxycycline, macrolides and clindamycin have been successfully used as alternatives [12, 16, 30, 31]. Few clinical data exist for treatment with newer β-lactam antibiotics, such as ceftriaxone [73, 77], piperacillin-tazobactam [78], imipenem [56] and meropenem [40].

The available data on antibiotic substances for treatment of pulmonary actinomycosis are summarised in table 4.

Treatment duration and monitoring

It has been suggested that the avascularity and induration of infected areas and the recognised relapse risk may account for the need for prolonged treatment of this infection [18]. Total durations of 6–12 months of antibiotic therapy have been recommended by recent reviews [1, 18, 20]. However, there is accumulating evidence that individualised shorter courses of treatment are associated with comparably good clinical outcomes in actinomycosis [4, 79]. This concept has also been adopted for treatment of pulmonary infections in more recent case series [10, 11, 16, 17, 31, 56]. The papers of HSIEH *et al.* [11], KOLDITZ *et al.* [16], SONG *et al.* [17] and CHOI *et al.* [31] report cumulatively on 92 patients who were exclusively medically treated, with median treatment durations between of 3 and 5.5 months and a high overall cure rate of >90%. YEW *et al.* [56] reported on eight patients with thoracic actinomycosis treated for only 4 weeks with intravenous imipenem, with a short-term cure rate of seven out of patients and a long-term cure rate of six out of seven patients. Two more series reported on patients failing medical treatment and requiring secondary surgical therapy. 1) DUJNEUNGKUNAKORN *et al.* [13] reported that two out of 10 patients

Table 4. Summary of data on antibiotic treatment for pulmonary actinomycosis

Agent	Susceptible species [22, 23]	Clinical evidence grade [ref.]
Preferred agents		
Benzylpenicillin	All	++ [5, 6, 11, 13, 16, 30, 31]
Amoxicillin ± clavulanic acid, ampicillin	All	++ [17, 30, 31]
Doxycycline	Most[#]	++ [16, 30]
Macrolides	Most[#]	++ [16, 30]
Clindamycin	Most[#]	++ [30, 31]
Probably effective agents		
Piperacillin/tazobactam	Most	+ [78]
Ceftriaxone	Most	+ [73, 77]
Imipenem/meropenem	Most	+ [40, 56]
Effective agents *in vitro*		
Tigecycline	All	No clinical data
Linezolid	Most	No clinical data
Ineffective agents *in vitro*		
Quinolones		
Vancomycin		
Aztreonam		
Aminoglycosides		
Metronidazole		

++: supported by recent case series and considerable successful clinical experience in other forms of actinomycosis; +: supported by anecdotal successful reports. [#]: occasional isolates of *Actinomyces turicensis* were found to be resistant to erythromycin and doxycycline and of *Actinomyces europaeus* were found resistant to erythromycin and clindamycin [22].

treated with intravenous penicillin showed recurrent haemoptysis or treatment failure after penicillin allergy. 2) SONG *et al.* [17] reported that five out of 23 patients treated with amoxicillin/clavulanic acid presented with treatment failure necessitating surgical removal of the core lesion after 3–8 months; however, two of them were treated only orally. All five patients showed an inadequate radiological response of the main lesion after treatment for 12 weeks, which was suggested to be a possible indicator for medical treatment failure. Additionally, failing patients had a significantly longer duration of symptoms prior to diagnosis (10 *versus* 2 months). Other clinical- or therapy-related factors to predict medical treatment failure could not be identified in this series. KOLDITZ *et al.* [16] reported that 46 medically treated patients showed a cure rate of 100% after treatment with antibiotics for a median of 4 months. Cure was defined as disappearance of clinical symptoms and disappearance or reduction to a residual scarring of the main lesions. However, during follow-up for a median of 27 months, the sustained cure rate was only 85% and, in six patients, infection recurrence or local infectious complications related to the former actinomycosis were noted. Five of these six patients had received antimicrobial treatment of <3 months, which suggested another risk factor for an unfavourable long-term outcome.

Thus, the risk of possible disease recurrence must be weighed against potential advantages of shorter treatment durations, such as decreased side-effects and costs. Response to treatment should be monitored both clinically and radiologically; a measurable response to treatment and diminution of the core lesion is expected within 4–8 weeks [17].

From these data, it can be concluded that although antibiotic therapy is effective and carries a high success rate, treatment failures during and after therapy can occur. Important factors to consider are radiographic evidence of reduction of the main lesion within the first 2–3 months during treatment and symptom duration prior to diagnosis. Individualised treatment durations below the recommended 6–12 months are associated with good outcomes, but antibiotic treatment should be applied at least until clinical and radiological disappearance of the infection is evident. Intensive clinical follow-up after the end of treatment, especially in patients treated for a short time (<3 months) and those with complicated disease presentation, is necessary to detect possible

disease recurrence or local complications. If medical treatment fails to achieve symptomatic and radiological improvement after 2–3 months, surgical debulking might be considered on an individual basis. Coexistent malignancy should be ruled out in case of treatment failure.

Surgical treatment

Primary surgical treatment should be reserved for patients presenting with massive haemoptysis or superinfected pleural effusion [1, 18, 80]. For pulmonary abscesses or fistulae, surgical treatment might be indicated on an individual basis. Otherwise antibiotic treatment is preferred. Nevertheless, in the majority of patients in recently reported case series, surgery was involved. The main diagnostic indication for surgery was the suspicion of malignancy after unsuccessful less invasive diagnostic attempts [81, 82]. Dependent on the localisation and size of the lesion, video-assisted thoracoscopic surgery (VATS) or thoracotomy have been performed, while VATS is preferentially indicated in smaller peripheral lesions.

If actinomycosis is diagnosed after surgical resection for supposed malignancy, antibiotic therapy is indicated similarly to medically treated patients. Inadequate antibiotic therapy post-operatively may result in complications, such as bronchopleural fistulae and empyema [1, 18]. Median post-operative treatment durations in recent series varied between 2.5 and 5 months [11, 12, 14, 15, 17, 31]. However, a significant proportion received short-term treatments of <3 months and even <4 weeks without reported treatment failures [17, 31]. Thus, the length of treatment can presumably be individualised similarly to medically treated patients, but antibiotics should be applied at least until complete symptom recovery and radiological clearance is evident. After complete resection of the lesion, short courses of 4 weeks might be sufficient for some cases if careful follow-up is provided.

Conclusion

Pulmonary actinomycosis is a rare, albeit important, disease because it clinically and radiologically mimics a variety of lung diseases including cancer and tuberculosis, but has a very good prognosis after antibiotic treatment. Diagnosis can be challenging, and is most important considering this infection, especially in patients with reported risk factors. Diagnostic confirmation requires bronchoscopic biopsy or transthoracic puncture and microbiological isolation of actinomycetes from infected tissue, but in everyday practice the histopathological evidence of sulfur granules is used as equivalent. High-dose and long-term penicillin treatment remains the therapy of choice, and clinical cure rates are very good. In the case of penicillin allergy, doxycycline, macrolides and clindamycin have been used successfully. Antibiotic treatment duration should be individualised according to the resolution of symptoms and radiological lesions, and the recommended period of 6–12 months often might not be necessary. Surgical treatment is reserved for patients developing complications, such as massive haemoptysis or empyema, and for those in whom a medical diagnosis cannot be established.

Statement of Interest

None declared.

References

1. Yildiz O, Doganay M. Actinomycoses and nocardia pulmonary infections. *Curr Opin Pulm Med* 2006; 12: 228–234.
2. Brook I. Actinomycosis: diagnosis and management. *South Med J* 2008; 101: 1019–1023.
3. Sullivan DC, Chapman SW. Bacteria that masquerade as fungi: actinomycosis/nocardia. *Proc Am Thorac Soc* 2010; 7: 216–221.
4. Wong VK, Turmezei TD, Weston VC. Actinomycosis. *BMJ* 2011; 343: d6099.
5. Bennhoff DF. Actinomycosis: diagnostic and therapeutic considerations and a review of 32 cases. *Laryngoscope* 1984; 94: 1198–1217.
6. Weese WC, Smith IM. A study of 57 cases of actinomycosis over a 36-year period. A diagnostic "failure" with good prognosis after treatment. *Arch Intern Med* 1975; 135: 1562–1568.

7. Pulverer G, Schutt-Gerowitt H, Schaal KP. Human cervicofacial actinomycoses: microbiological data for 1997 cases. *Clin Infect Dis* 2003; 37: 490–497.
8. Baldursdottir E, Jonasson L, Gottfredsson M. Hin morgu andlit geislagerlabolgu: Faraldsfraedileg rannsokn a Islandi 1984-2007. [The many faces of actinomycosis. Results from a retrospective study in Iceland, 1984–2007]. *Laeknabladid* 2010; 96: 323–328.
9. Brown JR. Human actinomycosis. A study of 181 subjects. *Hum Pathol* 1973; 4: 319–330.
10. Kinnear WJ, Macfarlane JT. A survey of thoracic actinomycosis. *Respir Med* 1990; 84: 57–59.
11. Hsieh MJ, Liu HP, Chang JP, *et al.* Thoracic actinomycosis. *Chest* 1993; 104: 366–370.
12. Rizzi A, Rocco G, Della PC, *et al.* Pulmonary actinomycosis: surgical considerations. *Monaldi Arch Chest Dis* 1996; 51: 369–372.
13. Dujneungkunakorn T, Riantawan P, Tungsagunwattana S. Pulmonary actinomycosis: a study of 16 cases from Central Chest Hospital. *J Med Assoc Thai* 1999; 82: 531–535.
14. Endo S, Murayama F, Yamaguchi T, *et al.* Surgical considerations for pulmonary actinomycosis. *Ann Thorac Surg* 2002; 74: 185–190.
15. Lu MS, Liu HP, Yeh CH, *et al.* The role of surgery in hemoptysis caused by thoracic actinomycosis; a forgotten disease. *Eur J Cardiothorac Surg* 2003; 24: 694–698.
16. Kolditz M, Bickhardt J, Matthiessen W, *et al.* Medical management of pulmonary actinomycosis: data from 49 consecutive cases. *J Antimicrob Chemother* 2009; 63: 839–841.
17. Song JU, Park HY, Jeon K, *et al.* Treatment of thoracic actinomycosis: A retrospective analysis of 40 patients. *Ann Thorac Med* 2010; 5: 80–85.
18. Mabeza GF, Macfarlane J. Pulmonary actinomycosis. *Eur Respir J* 2003; 21: 545–551.
19. Hall V. Actinomyces – gathering evidence of human colonization and infection. *Anaerobe* 2008; 14: 1–7.
20. Smego RA Jr, Foglia G. Actinomycosis. *Clin Infect Dis* 1998; 26: 1255–1261.
21. Tanaka-Bandoh K, Watanabe K, Kato N, *et al.* Susceptibilities of Actinomyces species and *Propionibacterium propionicus* to antimicrobial agents. *Clin Infect Dis* 1997; 25: Suppl. 2, S262–S263.
22. Smith AJ, Hall V, Thakker B, *et al.* Antimicrobial susceptibility testing of Actinomyces species with 12 antimicrobial agents. *J Antimicrob Chemother* 2005; 56: 407–409.
23. Hansen JM, Fjeldsoe-Nielsen H, Sulim S, *et al.* Actinomyces species: a Danish survey on human infections and microbiological characteristics. *Open Microbiol J* 2009; 3: 113–120.
24. Fujita Y, Iikura M, Horio Y, *et al.* Pulmonary *Actinomyces graevenitzii* infection presenting as organizing pneumonia diagnosed by PCR analysis. *J Med Microbiol* 2012; 61: 1156–1158.
25. Stingu CS, Rodloff AC, Jentsch H, *et al.* Rapid identification of oral anaerobic bacteria cultivated from subgingival biofilm by MALDI-TOF-MS. *Oral Microbiol Immunol* 2008; 23: 372–376.
26. Ng LS, Sim JH, Eng LC, *et al.* Comparison of phenotypic methods and matrix-assisted laser desorption ionisation time-of-flight mass spectrometry for the identification of aero-tolerant *Actinomyces* spp. isolated from soft-tissue infections. *Eur J Clin Microbiol Infect Dis* 2012; 31: 1749–1752.
27. Schaal KP, Lee HJ. Actinomycete infections in humans – a review. *Gene* 1992; 115: 201–211.
28. Cheon JE, Im JG, Kim MY, *et al.* Thoracic actinomycosis: CT findings. *Radiology* 1998; 209: 229–233.
29. Kim TS, Han J, Koh WJ, *et al.* Thoracic actinomycosis: CT features with histopathologic correlation. *AJR Am J Roentgenol* 2006; 186: 225–231.
30. Baik JJ, Lee GL, Yoo CG, *et al.* Pulmonary actinomycosis in Korea. *Respirology* 1999; 4: 31–35.
31. Choi J, Koh WJ, Kim TS, *et al.* Optimal duration of IV and oral antibiotics in the treatment of thoracic actinomycosis. *Chest* 2005; 128: 2211–2217.
32. Laish I, Benjaminov O, Morgenstern S, *et al.* Abdominal actinomycosis masquerading as colon cancer in a liver transplant recipient. *Transpl Infect Dis* 2012; 14: 86–90.
33. Klapholz A, Talavera W, Rorat E, *et al.* Pulmonary actinomycosis in a patient with HIV infection. *Mt Sinai J Med* 1989; 56: 300–303.
34. Cendan I, Klapholz A, Talavera W. Pulmonary actinomycosis. A cause of endobronchial disease in a patient with AIDS. *Chest* 1993; 103: 1886–1887.
35. Ossorio MA, Fields CL, Byrd RP Jr, *et al.* Thoracic actinomycosis and human immunodeficiency virus infection. *South Med J* 1997; 90: 1136–1138.
36. Garcia-Garcia JA, Corzo JE, Ramirez M, *et al.* Actinomicosis pulmonar con diseminacion hematogena en un paciente infectado por el virus de la inmunodeficiencia humana. [Pulmonary actinomycosis secondary bacteremia in a HIV-infected patient]. *Med Clin (Barc)* 2004; 123: 599.
37. Batt JA, Mullen JB, Vellend H, *et al.* Thoracic actinomycosis in a patient with pulmonary involvement caused by non-Hodgkin's lymphoma. *Clin Infect Dis* 1996; 22: 731–732.
38. Dentale N, Fulgaro C, Fasulo G, *et al.* Cervicofacial and pulmonary actinomycosis associated with non-Hodgkin's lymphoma. *Scand J Infect Dis* 1998; 30: 519–520.
39. Dolai TK, Kumar R, Chakrabarti P, *et al.* Actinomycetes species infection in a patient of T-cell acute lymphoblastic leukemia (ALL) presenting with loculated pleural effusion. *Pediatr Hematol Oncol* 2008; 25: 477–480.
40. Reichenbach J, Lopatin U, Mahlaoui N, *et al.* Actinomyces in chronic granulomatous disease: an emerging and unanticipated pathogen. *Clin Infect Dis* 2009; 49: 1703–1710.

41. Baron EJ, Angevine JM, Sundstrom W. Actinomycotic pulmonary abscess in an immunosuppressed patient. *Am J Clin Pathol* 1979; 72: 637–639.
42. Charalabopoulos K, Charalabopoulos AK, Papalimneou V, *et al.* Lung, pleural and colon actinomycosis in an immunocompromised patient: a rare form of presentation. *Chemotherapy* 2003; 49: 209–211.
43. Cohen RD, Bowie WR, Enns R, *et al.* Pulmonary actinomycosis complicating infliximab therapy for Crohn's disease. *Thorax* 2007; 62: 1013–1014.
44. Marie I, Lahaxe L, Levesque H, *et al.* Pulmonary actinomycosis in a patient with diffuse systemic sclerosis treated with infliximab. *QJM* 2008; 101: 419–421.
45. Bassiri AG, Girgis RE, Theodore J. Actinomyces odontolyticus thoracopulmonary infections. Two cases in lung and heart–lung transplant recipients and a review of the literature. *Chest* 1996; 109: 1109–1111.
46. Galaria II, Marcos A, Orloff M, *et al.* Pulmonary actinomycosis in solid organ transplantation. *Transplantation* 2003; 75: 1914–1915.
47. Han JY, Lee KN, Lee JK, *et al.* An overview of thoracic actinomycosis: CT features. *Insights Imaging* 2013; 4: 245–252.
48. Kim TS, Han J, Koh WJ, *et al.* Endobronchial actinomycosis associated with broncholithiasis: CT findings for nine patients. *AJR Am J Roentgenol* 2005; 185: 347–353.
49. Chouabe S, Perdu D, Deslee G, *et al.* Endobronchial actinomycosis associated with foreign body: four cases and a review of the literature. *Chest* 2002; 121: 2069–2072.
50. Bastian A, Khanavkar B, Scherff A, *et al.* Thorakale Aktinomykose: diagnostische Schwierigkeiten und therapeutische Überlegungen. [Thoracic actinomycosis: diagnostic pitfalls and therapeutic considerations]. *Pneumologie* 2009; 63: 86–92.
51. Wand A, Gilbert HM, Litvack B, *et al.* MRI of thoracic actinomycosis. *J Comput Assist Tomogr* 1996; 20: 770–772.
52. Andreani A, Rossi G, Giovannini M, *et al.* Unexpected positron emission tomography-positive actinomyces-related mass of the bronchial stump. *Can Respir J* 2012; 19: 77–79.
53. Hoekstra CJ, Hoekstra OS, Teengs JP, *et al.* Thoracic actinomycosis imaging with fluorine-18 fluorodeoxyglucose positron emission tomography. *Clin Nucl Med* 1999; 24: 529–530.
54. Severo LC, Kaemmerer A, Camargo JJ, *et al.* Actinomycotic intracavitary lung colonization. *Mycopathologia* 1989; 108: 1–4.
55. Sem LM, Arulananda S, Seow J, *et al.* Bronchoepidural fistula in a man with actinomycosis complicated non-small cell lung cancer. *J Thorac Oncol* 2011; 6: 1761–1762.
56. Yew WW, Wong PC, Lee J, *et al.* Report of eight cases of pulmonary actinomycosis and their treatment with imipenem-cilastatin. *Monaldi Arch Chest Dis* 1999; 54: 126–129.
57. Coodley EL, Yoshinaka R. Pleural effusion as the major manifestation of actinomycosis. *Chest* 1994; 106: 1615–1617.
58. Colice GL, Curtis A, Deslauriers J, *et al.* Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest* 2000; 118: 1158–1171.
59. Davies CWH, Gleeson FV, Davies RJO. BTS guidelines for the management of pleural infection. *Thorax* 2003; 58: 18ii.
60. Dalhoff K, Wallner S, Finck C, *et al.* Endobronchial actinomycosis. *Eur Respir J* 1994; 7: 1189–1191.
61. Seo JB, Lee JW, Ha SY, *et al.* Primary endobronchial actinomycosis associated with broncholithiasis. *Respiration* 2003; 70: 110–113.
62. Bergthorsdottir R, Benediktsdottir KR, Thorsteinsson SB, *et al.* Endobronchial actinomycosis secondary to a tooth aspiration. *Scand J Infect Dis* 2004; 36: 384–386.
63. Maki K, Shinagawa N, Nasuhara Y, *et al.* Endobronchial actinomycosis associated with a foreign body – successful short-term treatment with antibiotics. *Intern Med* 2010; 49: 1293–1296.
64. Hagan ME, Klotz SA, Bartholomew W, *et al.* Actinomycosis of the trachea with acute tracheal obstruction. *Clin Infect Dis* 1996; 22: 1126–1127.
65. Fernandez SH. Actinomycosis of the vocal cord: a case report. *Malays J Pathol* 1999; 21: 111–115.
66. Acevedo F, Baudrand R, Letelier LM, *et al.* Actinomycosis: a great pretender. Case reports of unusual presentations and a review of the literature. *Int J Infect Dis* 2008; 12: 358–362.
67. Fife TD, Finegold SM, Grennan T. Pericardial actinomycosis: case report and review. *Rev Infect Dis* 1991; 13: 120–126.
68. Peters GL, Davies RA, Veinot JP, *et al.* Cardiac actinomycosis: an unusual cause of an intracardiac mass. *J Am Soc Echocardiogr* 2006; 19: 1530–1511.
69. Kotoulas C, Foroulis C, Letsas K, *et al.* Thoracic actinomycosis as a cause of superior vena cava syndrome: report of a case. *Surg Today* 2004; 34: 447–449.
70. Zeebregts CJ, van der Heyden AH, Ligtvoet EE, *et al.* Transphrenic dissemination of actinomycosis. *Thorax* 1996; 51: 449–450.
71. Kim HS, Oh YW, Noh HJ, *et al.* Mycotic pulmonary artery aneurysm as an unusual complication of thoracic actinomycosis. *Korean J Radiol* 2004; 5: 68–71.
72. Miller AR, Robertson JM, Nelson RJ, *et al.* Pleuropulmonary actinomycosis associated with a systemic-to-pulmonary artery fistula and contralateral metastatic back mass. *Ann Thorac Surg* 1989; 47: 305–307.
73. Seo JY, Yeom JS, Ko KS. Actinomyces cardiffensis septicemia: a case report. *Diagn Microbiol Infect Dis* 2012; 73: 86–88.

74. Engelmann MG, Nikol S, Vogelmeier C. Pulmonary abscess with bacteremia in a young man. *CMAJ* 2004; 171: 233.
75. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–59.
76. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; 41: 580–637.
77. Skoutelis A, Petrochilos J, Bassaris H. Successful treatment of thoracic actinomycosis with ceftriaxone. *Clin Infect Dis* 1994; 19: 161–162.
78. Sando Y, Sugita Y, Kaneko K, *et al.* [Three cases of pulmonary actinomycosis]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1992; 30: 1869–1873.
79. Sudhakar SS, Ross JJ. Short-term treatment of actinomycosis: two cases and a review. *Clin Infect Dis* 2004; 38: 444–447.
80. Wohlgemuth SD, Gaddy MC. Surgical implications of actinomycosis. *South Med J* 1986; 79: 1574–1578.
81. Schweigert M, Meyer C, Stadlhuber RJ, *et al.* Surgery for inflammatory tumor of the lung caused by pulmonary actinomycosis. *Thorac Cardiovasc Surg* 2012; 60: 156–160.
82. Olmez OF, Cubukcu E, Evrensel T, *et al.* Pulmonary actinomycosis mimicking metastasis from lung adenocarcinoma. *Onkologie* 2012; 35: 604–606.

Chapter 8

Abscess of the lung: current therapeutic options

Kalliopi Athanassiadi[*], *Radoslav Jaković*[#] *and Nikolaos Siafakas*[¶]

SUMMARY: Lung abscess is a necrotising lung infection characterised by a pus-filled cavitary lesion and is potentially life threatening since it is often complicated to manage and difficult to treat. Lung abscess was a devastating disease in the pre-antibiotic era, when one-third of the patients died, another one-third recovered and the remainder developed debilitating illnesses, such as recurrent abscesses, chronic empyema, bronchiectasis or other consequences of chronic pyogenic infections. In the early post-antibiotic period, sulfonamides did not improve the outcome of patients with lung abscess until the penicillins and tetracyclines were available. Although resectional surgery was often considered a treatment option in the past, the role of surgery has greatly diminished over time because most patients with uncomplicated lung abscess eventually respond to prolonged antibiotic therapy.

[*]Dept of Thoracic Surgery, Evangelismos General Hospital, Athens, and
[¶]Dept of Pulmonary Medicine, University Hospital of Heraklion, Crete, Greece.
[#]Clinic of Thoracic Surgery, Clinical Center of Serbia, Belgrade, Serbia.

Correspondence: K. Athanassiadi, Konstantinoupoleosstr. 34A, 15562 Holargos, Athens, Greece.
Email: kallatha@otenet.gr

Eur Respir Monogr 2013; 61: 81–89.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041012
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Lung abscess is a necrotising lung infection characterised by a pus-filled cavitary lesion and is potentially life threatening since it is often complicated to manage and difficult to treat [1]. Prior to the availability of antibiotics, the clinical outcome of a patient with a lung abscess was fatal. 50 years ago, the mortality rate was greater than 50%, and many patients were left with significant residual symptomatic disease. However, in the modern era, it remains an important cause of mortality in the elderly and immunocompromised patients. The current management is primarily conservative medical treatment with surgery involved only in cases of antibiotic failure [2].

Classification

Lung abscesses are considered acute or chronic depending on the duration of symptoms at the time of presentation [1–3]. The arbitrary dividing time is 4–6 weeks. Primary lung abscesses are commonly observed in patients who are predisposed to aspiration or in otherwise healthy individuals, whereas secondary lung abscesses represent complications of a pre-existing condition (*e.g.* obstruction) or local lesion such as a bronchogenic carcinoma or a systemic disease (*e.g.* HIV infection) that compromises immune function. Lung abscesses can be further characterised by the responsible pathogen, such as *Staphylococcus* lung abscess and anaerobic or *Aspergillus* lung abscess.

Pathophysiology

The common causes of primary lung abscesses are aspiration, necrotising pneumonia and immunodeficiency [1, 4, 5]. Before the availability of antibiotics, the aetiology of a typical abscess was complications after oral surgical procedures (*i.e.* tonsillectomy), resulting in aspiration of infected material into the lungs. In the absence of satisfactory antibiotic treatment, this event usually led to a lung abscess or to a necrotising pneumonia with or without pleural empyema.

In cases of aspiration of oropharyngeal flora there is a predilection for dependent areas as the posterior segment of the right upper lobe, the superior segments of both lower lobes and other lower lobe segments. Aspiration may occur in the setting of impaired consciousness, alcoholism, gastro-oesophageal reflux disease and other dysphagia syndromes, such as stricture, Zenker's diverticulum, *etc.* Poor dental hygiene, gingival disease and high bacterial counts in gingival crevices are also common [2, 4].

In necrotising pneumonia followed by destruction of lung parenchyma, commonly mixed anaerobe and aerobic flora are present. The environment in which aspiration occurs also reflects, for instance, hospital or nursing home flora colonisation [3, 5, 6].

The most common causes of secondary abscesses are endobronchial obstruction (neoplasms, foreign bodies) and external bronchial compression, while secondary infection of pre-existing cavity (emphysema bullae, cysts, resolving lung infarct, cavitating neoplasm) are not true abscesses but manifest in a similar fashion and one should take them into account in the differential diagnosis and consequent treatment. Lung abscess may also occur secondary to extension of infection from nearby infected areas (mediastinum, chest wall, diaphragm, or infradiaphragmatic locations) (table 1) [6–8].

Table 1. Entities affecting differential diagnosis of a lung abscess as a cavitating pulmonary lesion

Infectious diseases
Aspergillosis
Histoplasmosis
Nocardiosis
Cryptococcosis
Coccidioidomycosis
Tuberculosis
Atypical mycobacterial disease
Necrotising bacterial pneumonia
Loculated empyema
Neoplasms
Bronchogenic carcinoma
Metastatic carcinoma
Lymphoma
Inflammatory diseases
Granulomatosis with polyangiitis (Wegener's)
Rheumatoid nodule
Miscellaneous
Blant pulmonary infarct
Pneumatocoele (post-infectious or traumatic)
Sarcoidosis (rare)
Silicosis
Developmental lesions
Bronchogenic cyst
Pulmonary sequestration
Cystic adenomatoid malformation
Diaphragmatic hernia

Microbiology

The most common pathogens of lung abscesses due to aspiration are anaerobic bacteria, but about half of all cases involve both anaerobic and aerobic organisms [1, 3, 6, 7, 9]. The most common aerobic pathogens are streptococci and staphylococci, sometimes methicillin-resistant *Staphylococcus aureus* (MRSA). An unusual but very important acute and often lethal form of lung necrosis is caused by *S. aureus*, whereas very serious and fulminant cases may be caused by MRSA, which has become a rare but very important cause of necrotising pneumonia in young, previously healthy adults and children. Occasionally, cases are due to Gram-negative bacteria, especially *Klebsiella*. Immunocompromised patients with lung abscess may have infection with *Nocardia*, *Mycobacteria* spp., or fungi. Some people, especially those from developing countries, are at risk of abscess due to *Mycobacterium tuberculosis*, and rare cases are due to amoebic infection (*e.g.* with *Entamoeba histolytica*), *Paragonimiasis* or *Burkholderia pseudomallei* [10]. Hospital-acquired Gram-negative infections are usually due to nosocomial organisms (*e.g. Pseudomonas*, *Enterobacter*,

Proteus). Patients with these infections are often elderly, debilitated with numerous major medical disorders or have sustained multiple trauma. These patients are typically treated in a critical care unit.

The infection is usually due to a resistant organism originating from a single source. The lung abscess appears rapidly as an area of pneumonitis with associated pleural involvement. These patients often require percutaneous drainage as an emergency procedure. Unfortunately, the infection is systemic and often out of control, and the pulmonary pathology represents only one aspect of a multiorgan involvement with a rapidly deteriorating course [4, 5].

Among fungal infections, *Aspergillus* has become a major organism in lung abscesses. Fungal infections are difficult to treat, and amphotericin/fluconazole and surgical drainage remain the only modalities of treatment; however, at best, they have had only limited success [7].

Symptoms and signs

Generally, most of the patients admitted to the hospital with a diagnosis of lung abscess have had symptoms for at least 2 weeks. These patients typically have an intermittent febrile course, productive cough, weight loss, general malaise and night sweats [1, 4, 8]. Initially, foul sputum is not observed in the course of the infection; however, after cavitation occurs, putrid expectorations are quite prevalent. Haemoptysis may occasionally follow the expectoration of putrid sputum [11]. The physical findings are similar to those of pneumonia, with or without a pleural effusion. Auscultation may reveal coarse bronchi and absent breath sounds. Clubbing of the fingers is sometimes noted.

Symptoms of abscess due to anaerobic bacteria or mixed anaerobic and aerobic bacteria are usually chronic (*e.g.* over weeks or months) and include productive cough, fever, sweats and weight loss. Severe prostration may occur [8, 12]. Sputum may be purulent or blood-streaked and classically smells or tastes foul. Symptoms of abscess due to aerobic bacteria develop more acutely and resemble bacterial pneumonia [1, 4]. Abscesses due to organisms other than anaerobes (*e.g.* *Mycobacteria*, *Nocardia*) lack putrid respiratory secretions and may be more likely to occur in nondependent lung regions.

Diagnosis

Lung abscess is suspected based on history and is confirmed by chest radiograph. In an anaerobic infection due to aspiration, chest radiograph classically shows consolidation with a single cavity containing an air-fluid level in portions of the lung that would be dependent when the patient is recumbent (*e.g.* the posterior segments of the upper lobes or the superior or lateral basal segments of the lower lobes). This pattern helps distinguish anaerobic abscess from other causes of cavitary pulmonary disease, because diffuse or embolic pulmonary disease often causes multiple cavitations, and tuberculosis typically involves the apices. One has to take into account that the chest radiograph is not pathognomonic in the early stages (fig. 1).

Computed tomography (CT) is not routinely needed but is useful for differential diagnosis, for instance, when the radiograph suggests a cavitating lesion or when an underlying pulmonary mass obstructing the drainage of a lung segment is suspected. Obviously, it should be always performed in smokers, recent smokers and patients with unexplained cavitary lesions and no fever (fig. 2).

Invasive diagnostic techniques occasionally recommended to diagnose lung abscesses include transtracheal aspirates, transthoracic aspirates and fibre-optic bronchoscopy [4]. These procedures must be performed prior to the institution of antibiotic therapy in order to acquire dependable microbiological data. The indications and comparative benefits of such procedures are controversial and depend to a great extent on operator ability. Bronchoscopy is considered to be the diagnostic tool of choice since it is also performed in order to exclude cancer or the presence of a foreign body or to detect unusual pathogens, such as fungi.

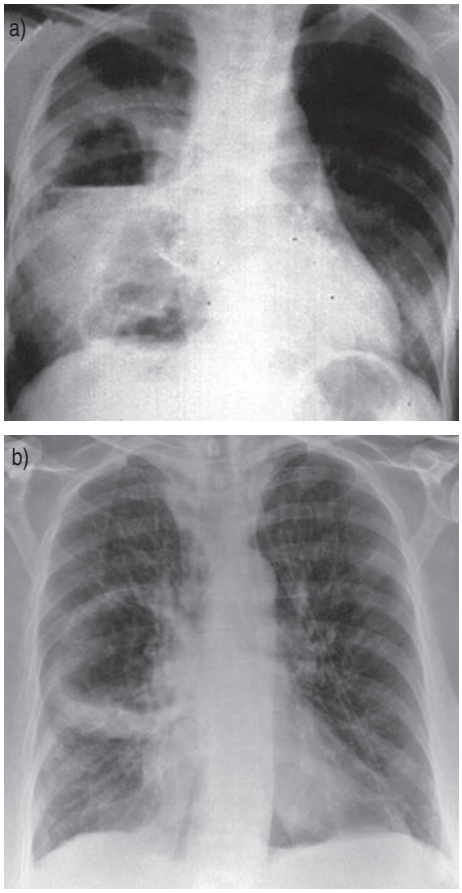


Figure 1. Chest radiographs showing a) the classical appearance of a pulmonary abscess as a cavity containing an air-fluid level, and b) pneumonia complicated by a lung abscess with a thick wall and ill-defined irregular margins.

Cultures

Evaluation of expectorated sputum (cultures) is the first step in the diagnosis of a patient with a lung abscess (unless anaerobic infection is very likely) [1, 6]. When clinical findings make anaerobic infection less likely, aerobic, fungal or mycobacterial infection should be suspected, and attempts should be made to identify a pathogen. Cultures of sputum, bronchoscopic aspirates or both are helpful. MRSA is generally found in both the sputum and blood cultures.

Treatment

Medical treatment

The implementation of the appropriate antimicrobial therapy is the cornerstone of medical treatment of lung abscesses. Around 1946, management of pulmonary abscess with antibiotics changed the clinical course of the disease [13]. Sulfonamides had shown disappointing results, but penicillin revolutionised the therapy of lung abscess showing good results [14, 15]. The advent of penicillin not only overthrew the surgical treatment of lung abscess, but it also brought about a substantial decline in its incidence.

A series of 115 cases of acute lung abscess collected between the years 1943 and 1956 treated either medically or surgically in case of failing medical therapy presented a mortality reduced to 6.9–8.7% [13, 16]. Unfortunately, the overall efficacy of penicillin seemed to diminish with time [3, 6], while tetracycline was considered inadequate therapy, because most anaerobes were resistant to it. Alternatively, although metronidazole is an effective drug against anaerobic bacteria, the experience in treating lung abscess had been rather disappointing with a failure rate of 50%, because these infections are generally polymicrobial [17].

The current management of anaerobic lung abscesses includes prolonged antibiotic therapy. The standard treatment of an anaerobic lung infection is clindamycin (600 mg *i.v.* every 8 h followed by 150–300 mg orally four times a day). This regimen has been shown to be superior over parenteral penicillin in published trials, since several anaerobes may produce β-lactamase (*e.g.* various species of Bacteroides and Fusobacterium) and therefore develop resistance to penicillin. In hospitalised patients who have aspirated and developed a lung abscess, antibiotic therapy should include coverage against *S. aureus* and *Enterobacter* and *Pseudomonas* spp. ALLEWELT *et al.* [18], in a prospective, open, randomised, comparative multicentre trial, compared the safety, clinical and bacteriological efficacy of ampicillin+sulbactam *versus* clindamycin ± cephalosporin. Ampicillin/sulbactam as a β-lactam/β-lactamase inhibitor combination with a broad spectrum of antibacterial activity against Gram-positive, Gram-negative and anaerobic bacteria in a 2:1 ratio has proved to be a significant drug in the therapeutic armamentarium for lower respiratory tract infections, aspiration pneumonia and lung abscess, well tolerated and as effective as clindamycin with or without a cephalosporin in the treatment of aspiration pneumonia [18, 19]. Additionally, OTT *et al.* [20] proved in a prospective trial that moxifloxacin appears to be clinically as effective

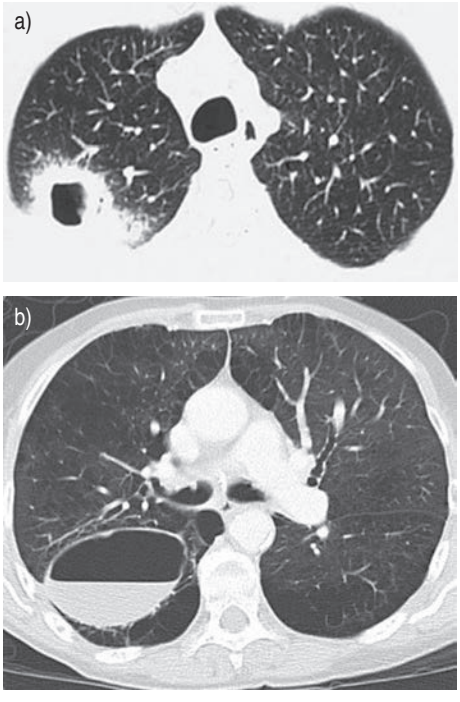


Figure 2. Computed tomography scans showing a) a thin-walled cavity with surrounding consolidation, and b) a lung abscess with a characteristic air-fluid level.

and as safe as ampicillin/sulbactam; however, having the benefit of a more convenient treatment (400 mg once a day) [20].

Duration of therapy

Optimal duration of medical treatment is unknown, but common practice is to treat until the chest radiograph shows complete resolution, which generally takes 3–6 weeks or longer. In general, the larger the abscess, the longer it will take for radiographs to show resolution. Expert opinion suggests that antibiotic treatment should be continued until the chest radiograph has shown either the resolution of lung abscess or the presence of a small stable lesion. The rationale for extended treatment is that it avoids the risk of relapse, which exists with a shorter antibiotic regimen.

Response to therapy

Patients with lung abscesses usually show clinical improvement, with improvement of fever, within 3–4 days after initiating the antibiotic therapy. Apyrexia is expected in 7–10 days. Persistent fever beyond this time indicates therapeutic failure and these patients should undergo further diagnostic studies to determine the cause of failure.

Considerations in patients with poor response to antibiotic therapy include bronchial obstruction with a foreign body or neoplasm or infection with a resistant bacteria, mycobacteria or fungi.

Large cavity size (*i.e.* >6 cm in diameter) usually requires prolonged therapy. Because empyema with an air-fluid level could be mistaken for parenchymal abscess, a CT scan may be used to differentiate this process from lung abscess.

A nonbacterial cause of cavitary lung disease may be present, such as lung infarction, cavitating neoplasm and vasculitis. The infection of a pre-existing sequestration, cyst or bulla may be the cause of delayed response to antibiotics.

Because effective broad-spectrum antibiotics are available, primary or nonspecific abscesses can frequently be arrested in the early stage of suppurative pneumonitis. Intravenous therapy is appropriate for adults until an initial clinical response is observed, after this time, oral therapy is safe.

After initial antibiotic therapy, the clinical and radiographic response is gradual, but normalisation of the chest radiograph may require 2 months [4, 8].

Drainage

Most lung abscesses communicate with the tracheobronchial tree early in the course of the infection and drain spontaneously during the course of therapy. Chest physical therapy and postural drainage because they may cause spillage of infection into other bronchi or acute obstruction are controversial. Dependent drainage (with appropriate positions based on the pulmonary segment) is commonly advocated using chest physical therapy and sometimes bronchoscopy can also facilitate abscess drainage by aspiration of the appropriate bronchus through the bronchoscope [2, 4]. Transbronchial drainage by catheterisation of the appropriate bronchus under fluoroscopy has been successful.

Generally, augmenting this passive drainage with invasive procedures is unnecessary. In fact, manipulations during therapeutic bronchoscopy may sometimes produce adverse consequences. Reports have been received of bronchoscopy-induced release of large amounts of purulent material from the involved lung segment into other parts of the lung, occasionally inducing acute respiratory failure, acute respiratory distress syndrome (ARDS) or both. Recently, lasers have also been used for endobronchial drainage of lung abscess. Lasers can perforate the wall through the airways and provide a route for catheter drainage [21]. If the patient is weak or paralysed or has respiratory failure, tracheostomy and suctioning may be necessary, while bronchoscopic aspiration may facilitate drainage.

Percutaneous drainage

Percutaneous drainage of a complicated abscess (*i.e.* one associated with fever and signs of sepsis) is beneficial in selected patients who do not respond to adequate medical therapy [22]. These are ventilator-dependent patients who are not candidates for extensive thoracic procedures. Other indications for drainage include ongoing sepsis despite adequate antimicrobial therapy, progressively enlarging lung abscess in imminent danger of rupture, failure to wean from mechanical ventilation and contamination of the opposite lung. In current practice, most of these lung abscesses are drained under CT or ultrasound guidance [22, 23].

Results achieved with percutaneous drainage show it to be safe and effective compared with surgery. Percutaneous drainage is rarely complicated by empyema, haemorrhage or bronchopleural fistula (BPF) or pneumothorax. Although a few patients develop BPF, most of these fistulae close spontaneously with resolution of the abscess cavity. Percutaneous drainage may also be used to stabilise and prepare critically ill patients for surgery.

Surgical drainage

Modern history of surgery for primary lung abscess begins with the dawn of thoracic surgery in the first decades of the 20th century [16]. Neuhof was the first thoracic surgeon to develop a valid and reliable therapeutic concept for surgery of acute pulmonary abscess by proposing an entirely new one-stage open drainage operation for lung abscess decreasing in that way mortality at 2.4% [24, 25]. Because of the emergence of acquired immunodeficiency syndrome, the technique of Neuhof was once more remembered by POSTMA *et al.* [26] who published between the years 1978 and 1984, 68 cases treated by open drainage without need of later pulmonary resection. In that way, the authors managed to decrease mortality and morbidity to 0.9% and they consider the open drainage to be an alternative treatment in patients too sick to undergo pulmonary resection.

Surgical treatment

Surgical treatment is now rarely necessary and is almost never the initial choice in the treatment of lung abscesses. In current practice, fewer than 15% of patients need surgical intervention for the uncontrolled disease and for complications that occur in both the acute and chronic stages of the disease. Currently, it is reserved for specific indications such as little or no response to medical treatment, inability to eliminate a carcinoma as a cause, critical haemoptysis and complications of lung abscess (*e.g.* empyema, BPF). In addition, if after 4–6 weeks of medical treatment a notable residual cavity remains and the patient is symptomatic, surgical resection is advocated [16].

Several important factors must be considered prior to undertaking surgery. Because of the high risk of spillage of the abscess into the contralateral lung, it is almost essential that a double-lumen tube be used to protect the airway [27]. If this is not available, surgery poses a very high risk of abscess in the other lung and a risk of ARDS. In such cases, postponing the surgery is a wise decision. Another less-satisfactory method to deal with this problem includes positioning the patient in the prone position. The surgeon must be skilled in resecting the abscess and in rapid

clamping of the bronchus to prevent spillage into the trachea. These factors are extremely important when dealing with the surgical aspects of treating a lung abscess.

Lobectomy is the most common procedure, while segmental resection may suffice for small lesions (<4 cm diameter cavity). In very rare cases with multiple abscesses or with pulmonary gangrene unresponsive to drug therapy, pneumonectomy may be necessary (fig. 3) [2, 12, 16].

The results of surgery are difficult to assess because of the varying patient population and the tremendous increase in illicit drug abuse, alcoholism, AIDS and infections by Gram-negative and opportunistic organisms. These factors have increased the incidence of lung abscess and the associated morbidity nowadays.

Although thoracotomy is the approach of choice recently, video-assisted thoracoscopic surgery has been successfully used by NAGASAWA *et al.* [28] showing that thoracoscopic surgery can lead to effective drainage of paediatric lung abscess without major complications. In addition, other benefits of thoracoscopy include rapid recovery, less pain and minimal morbidity.

Complications

Approximately one-third of lung abscesses are complicated by empyema. This may be observed with or without BPF. Haemoptysis is a common complication of a lung abscess and can be treated with bronchial artery embolisation. Occasionally, the haemoptysis can be massive, thus requiring urgent surgery. Brain abscess may also be a complication in patients who receive inadequate treatment.

Prognosis

The prognosis of patients with lung abscesses depends on the underlying or predisposing pathologic event and the speed with which appropriate therapy is established. Negative prognostic factors include a large cavity (>6 cm), necrotising pneumonia, multiple abscesses, immunocompromised patients, age extremes, associated bronchial obstruction and aerobic bacterial pneumonia. The mortality rate associated with an anaerobic lung abscess is less than 15%, although it is slightly higher in patients with necrotising anaerobic pneumonia and pneumonia caused by Gram-negative bacteria [29]. The prognosis associated with amoebic lung abscess is good when treatment is prompt. Overall, lung abscess can have a better prognosis and shorter length of hospital admission if the diagnosis is made promptly and a consensus on antibiotics is available.

Conclusion

If treatment is started in the acute stage of the disease and is continued for 4–6 weeks, approximately 85–95% of patients with anaerobic lung abscesses respond to medical management alone. Successful medical therapy resolves symptoms with no radiographic evidence or only a residual thin-walled cystic cavity (<2 cm).

The success of medical therapy is dependent on the duration of symptoms and the size of the cavity before the initiation of therapy. Antibiotic therapy is rarely

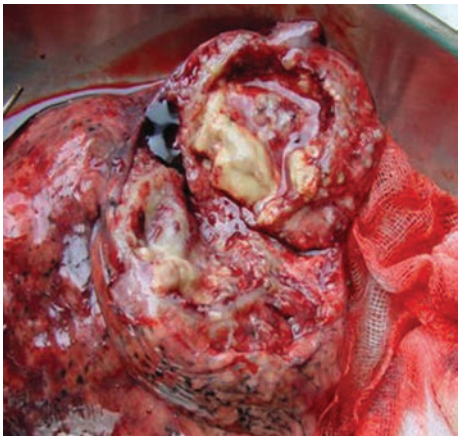


Figure 3. Operative lung specimen with gangrene complicating the lung abscess.

successful if symptoms are present for longer than 12 weeks before the initiation of treatment or if the original diameter of the cavity is more than 4 cm. When patients with lung abscesses do not respond to proper medical therapy, one should consider the probability of surgery with lobectomy being the most common procedure.

Statement of Interest

N. Siafakas received consultancy fees from Novartis Hellas.

References

1. Bartlett JG. Lung abscess. *In:* Baum GL, Wolinsky E, eds. Textbook of Pulmonary Diseases, 5th Edn. Boston, Little, Brown 1994; pp. 607–620.
2. Merritt RE, Shrager JB. Indications for surgery in patients with localized pulmonary infection. *Thorac Surg Clin* 2012; 22: 325–332.
3. Bartlett JG. Antibiotics in lung abscess. *Semin Respir Infect* 1991; 6: 103–111.
4. Davis B, Systrom DM. Lung abscess: pathogenesis, diagnosis and treatment. *Curr Clin Topics Infect Dis* 1998; 18: 252–273.
5. Magalhaes L, Valadares D, Oliveira JR, *et al.* Lung abscesses: review of 60 cases. *Rev Port Pneumol* 2009; 15: 165–178.
6. Bartlett JG. Bacteriologic diagnosis in anaerobic pleuropulmonary infections. *Clin Infect Dis* 1993; 16: Suppl. 4, S443–S445.
7. Bartlett JG, Gorbach SL, Tally FP, *et al.* Bacteriology and treatment of primary lung abscess. *Am Rev Respir Dis.* 1974; 109: 510–518.
8. Hood MR. Bacterial diseases of the lung. *In:* Shields TW, ed. General Thoracic Surgery. 4th Edn. Philadelphia, Lea & Febiger 1989; pp. 751–771.
9. Takayanagi N, Kagiyama N, Ishiguro T, *et al.* Etiology and outcome of community-acquired lung abscess. *Respiration* 2010; 80: 98–105.
10. Adebonojo SA, Grillo IA, Osinowo O, *et al.* Suppurative diseases of the lung and pleura: a continuing challenge in developing countries. *Ann Thorac Surg* 1982; 33: 40–47.
11. Philpott NJ, Woodhead MA, Wilson AG, *et al.* Lung abscess: a neglected cause of life threatening haemoptysis. *Thorax* 1993; 48: 674–675.
12. Jaroszewski DE, Webb BJ, Leslie KO. Diagnosis and management of lung infections. *Thorac Surg Clin* 2012; 22: 301–324.
13. Schweppe HI, Knowles JH, Kane L. Lung abscess. An analysis of the Massachusetts General Hospital cases from 1943 through 1956. *N Engl J Med* 1961; 265: 1039–1043.
14. Stivelman BP, Kavee J. Penicillin in the treatment of putrid lung abscess. *Ann Intern Med* 1946; 25: 66–77.
15. Stivelman BP, Kavee J. The treatment of acute putrid lung abscess with penicillin and sulfadiazine. *Ann Intern Med* 1949; 30: 343–363.
16. Schweigert M, Dubecz A, Stadlhuber RJ, *et al.* Modern history of surgical management of lung abscess: from Harold Neuhof to current concepts. *Ann Thorac Surg* 2011; 92: 2293–2297.
17. Perlino CA. Metronidazole *versus* clindamycin treatment of anerobic pulmonary infection. Failure of metronidazole therapy. *Arch Intern Med* 1981; 141: 1424–1427.
18. Allewelt M, Schuler P, Bolcskei PL, *et al.* Ampicillin+sulbactam *versus* clindamycin ± cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. *Clin Microbiol Infect* 2004; 10: 163–170.
19. Rafailidis PI, Ioannidou EN, Falagas ME. Ampicillin/sulbactam: current status in severe bacterial infections. *Drugs* 2007; 67: 1829–1849.
20. Ott SR, Allewelt M, Lorenz J, *et al.* Moxifloxacin *versus* ampicillin/sulbactam in aspiration pneumonia and primary lung abscess. *Infection* 2008; 36: 23–30.
21. Shlomi D, Kramer MR, Fuks L, *et al.* Endobronchial drainage of lung abscess: the use of laser. *Scand J Infect Dis* 2010; 42: 65–68.
22. Kelogrigoris M, Tsagouli P, Stathopoulos K, *et al.* CT-guided percutaneous drainage of lung abscesses: review of 40 cases. *JBR-BTR* 2011; 94: 191–195.
23. Vansonnenberg E, D'agostino HB, Casola G, *et al.* Lung abscess: CT-guided drainage. *Radiol* 1991; 178: 347–351.
24. Neuhof H, Touroff AS, Aufses AH. The surgical treatment, by drainage, of subacute and chronic putrid abscess of the lung. *Ann Surg* 1941; 113: 209–220.
25. Shaw RR, Paulson DL. Pulmonary resection for chronic abscess of the lung. *J Thorac Surg* 1948; 17: 514–522.
26. Postma MH, Le Roux BT. The place of external drainage in the management of lung abscess. *S Afr J Surg* 1986; 24: 156–158.

27. Pfitzner J, Peacock MJ, Tsirgiotis E, *et al.* Lobectomy for cavitating lung abscess with haemoptysis: strategy for protecting the contralateral lung and also the non-involved lobe of the ipsilateral lung. *Br J Anaesth* 2000; 85: 791–794.
28. Nagasawa KK, Johnson SM. Thoracoscopic treatment of pediatric lung abscesses. *J Pediatr Surg* 2010; 45: 574–578.
29. Hirshberg B, Sklair-Levi M, Nir-Paz R, *et al.* Factors predicting mortality of patients with lung abscess. *Chest* 1999; 115: 746–750.

Chapter 9

Surgical treatment of bronchiectasis

Dragan Subotic[*] *and Didier Lardinois*[#]

SUMMARY: The role of surgery for the treatment of the localised form of bronchiectasis has changed with the development of more effective antibiotics and conservative treatment options, such as embolisation or effective novel anti-inflammatory treatment approaches in subjects with cystic fibrosis (CF) and non-CF bronchiectasis, as suggested recently. However, surgery is the only option for a potential cure for certain patients with bronchiectasis. Complete resection of bronchiectasis should be intended with the preservation of as much lung function as possible. Incomplete resection is often used for the palliative treatment of life-threatening symptoms, *e.g.* major haemoptysis.

The usual clinical problems in patients undergoing surgery for bronchiectasis are bilateral bronchiectasis, haemoptysis and previous pleural empyema. The outcome for surgical treatment is good, with a low operative mortality and morbidity rate; however, higher than reported for non-infectious pathology. Complications of surgery usually range between 10% and 25% and largely consist of a prolonged air leak, bleeding, empyema and/or respiratory failure. In most series, lobectomy is the commonest type of resection with a rate of approximately 60%. Video-assisted thoracoscopic surgery for pulmonary resection has become an established alternative approach to conventional open surgery for selected patients.

The educational aim of this chapter is to provide a comprehensive overview of the possible solutions to the most frequent practical problems encountered by patients who have a localised form of bronchiectasis and are being considered for surgical treatment.

[*]Clinic for Thoracic Surgery, Clinical Center of Serbia, University of Belgrade, School of Medicine, Belgrade, Serbia.
[#]Dept of Thoracic Surgery, University Hospital Basel, Basel, Switzerland.

Correspondence: D. Subotic, Clinic for Thoracic Surgery, Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia. Email: profsubotic@gmail.com

Eur Respir Monogr 2013; 61: 90–106.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041212
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Epidemiology

The prevalence of bronchiectasis in industrialised countries has declined significantly (estimated as <0.6 per 1000 population), but in developing countries it is still a major cause of morbidity and mortality [1]. The common feature, irrespective of country, is that a relatively small number of patients with bronchiectasis have a disproportionate share of the overall medical care utilisation,

which includes inpatient care, outpatient care and drug therapy [2]. Recent evidence demonstrates that the epidemiology of bronchiectasis is changing towards the more advanced age groups, with this comes an increasing trend towards hospitalisation and healthcare utilisation for the patients [3, 4].

Currently, in developed countries, surgical treatment is necessary in the minority of patients with bronchiectasis. FUJIMOTO *et al.* [5] found that the percentage was 18.3% in the Ruhrlandklinik Hospital (Essen, Germany), and AGASTHIAN *et al.* [1] reported it as low as 3.9% in the Mayo Clinic (Rochester, MN, USA).

The emergence of drug-resistant micro-organisms and increasing frequency of multidrug-resistant tuberculosis (TB) are reasons for the increase in bronchiectasis in developing countries. Irregular and inadequate treatment, the cessation of medication shortly after symptom improvement, as well as the lack of check-ups post treatment, are all reasons for the recurrence of pulmonary infections in these patients.

A high incidence of bronchiectasis has recently been reported in chronic obstructive pulmonary disease (COPD) patients, up to 29–50% of the investigated patients [6]. These patients had more dyspnoea and worse lung functions than in the bronchiectasis-free COPD group of patients [7, 8].

Demographics, according to published surgical series with localized form of the disease, are presented on table 1. It is important to note that the female sex and younger age group are predominant in the majority of the reported series.

Morphology: indications for surgery

According to widely used morphological classifications, bronchiectasis can be divided into cylindrical, saccular, and varicose varieties. However, morphology itself is not essential in terms of deciding surgery. Cylindrical type is often regarded as an early bronchiectatic change that can be reversible.

The localised form of bronchiectasis is predominantly left-sided, involving most frequently lower lobes. Bilateral disease exists in 9–21% of patients. Unilateral bronchiectasis may affect one or more lobes. The same distribution may exist in cases of bilateral disease.

Although the duration for symptoms, in most patients who have been operated on, is only several years, in approximately 10% of patients no prior symptoms exist, so that they first present with haemoptysis, lung abscess, or an unresolved pneumonia. This fact, together with a wide range in years for symptom duration as reported in the studies cited in table 1 (0–50 years [5], 2–30 years [9], and 1–40 years [10]), contributes to the overall challenge of bronchiectasis as a clinical problem.

Before 1995, bronchography was a widely accepted diagnostic tool in patients with suspected bronchiectasis (fig 1a). After 1995, high-resolution computed tomography (HRCT) scans became a diagnostic standard, with 2% false-negative and 1% false-positive results [15–18]. The main CT criteria for diagnosis of bronchiectasis are internal diameter of the bronchus more than 1.5 times than that of accompanying artery and evidence of lack of tapering of bronchi, false-positive and false-negative rates are 2% and 1%, respectively [19].

Table 1. Demographics of bronchiectasis

First author [ref.]	Year	Subjects n	Female %	Age years
FUJIMOTO [5]	2001	90	51.1	44.7
KUTLAY [9]	2002	166	55.4	34.1 (7–70)
PRIETO [10]	2001	119	60	42.2 (11–77)
NICOTRA [11]	1995	123	69	57.2±16.7
ASHOUR [12]	1999	85	32	29.4±9.7[#]
BALKANLI [13]	2003	238	14	23.7 (15–48)
MANDARIC [14]	1983	145	47	NA[¶]

Data are presented as mean, mean (range) or mean±SD, unless otherwise stated. NA: not available. [#]: 84.7% aged <40 years; [¶]: 71.7% aged <40 years.

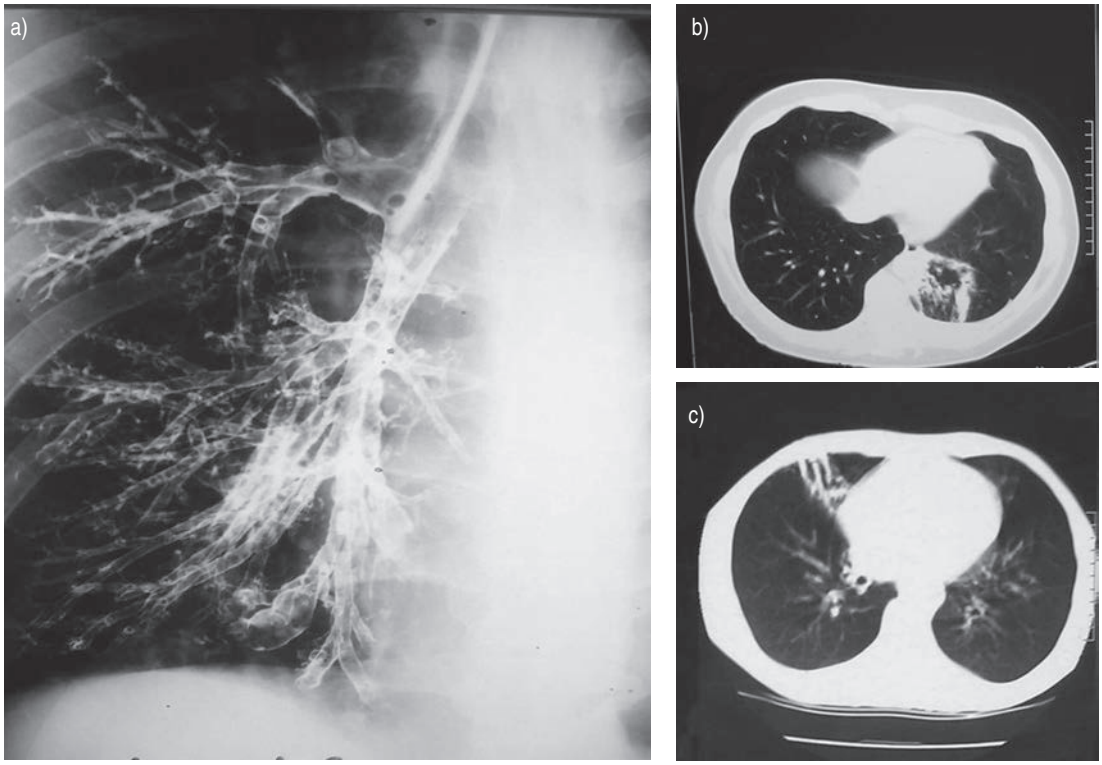


Figure 1. Imaging of patients with bronchiectasis. a) Bronchography showing a right lower lobe bronchiectasis. b) A computed tomography (CT) image showing a left lower-lobe bronchiectasis. c) A CT image showing a ''tram-tracks'' sign.

Apart from the typical aspect of bronchiectasis (fig. 1b), a so-called ''tram-tracks'' sign may also be present (fig. 1c).

If some initial concerns existed, related to the ability of CTs to assess the spatial distribution of bronchiectasis in comparison with bronchography, new generations of CTs have alleviated this concern. Modern software provides detailed and reliable information concerning the morphology and distribution of the areas within the diseased lung, so that surgical treatment can be adequately planned.

In all candidates proposed for surgery, a fibre-optic bronchoscopy is mandatory with a twofold aim of 1) ruling out the underlying endobronchial lesion and 2) assessing the degree of inflammation. In addition, a bronchoscopy gives an insight into the level of origin of lobar and segmental bronchi that is very important for planning of the subsequent resection.

The rationale for surgery in patients with bronchiectasis is not only the removal of segments, which are no longer functional, but also to prevent the infectious contamination of the adjacent zones within the lung.

As presented in table 2, recurrent infections are, by far, the most frequent indication for the need for an operation, followed by haemoptysis and an abscess. Sometimes, patients with bronchiectasis are operated upon because of undiagnosed lung masses.

The aforementioned wide range in time for symptom duration before surgery is undertaken, in the presence of a recurrent infection, is caused by the impossibility of establishing the precise criteria in which an operation should occur, due to the decision being largely based upon the patient's degree of discomfort in their private and/or professional life. The situation becomes clearer in the presence of a haemoptysis, where symptom duration is significantly shorter before the operation.

Table 2. Indications for the need to operate on patients with bronchiectasis

	Fujimoto [5]	Balkanli [13]	Kutlay [9]	Prieto [10]	Agasthian [1]
Year	2001	2003	2002	2001	1996
Patients	92	238	166	119	134
Recurrent infections	57 (62.2)	163 (68.4)	158 (95.2)	65 (55)	85 (63.4)
Haemoptysis	22 (23.3)	39 (16.4)	5 (3)	31 (26.5)	26 (19.4)
Abscess	9 (10)	NA	3 (1.8)	10 (9)	12 (9)
Undiagnosed lung mass	3 (3.3)	NA	NA	9 (8)	11 (8.2)
Pneumothorax	NA	NA	NA	4 (3)	NA
Empyema	1 (1.1)	NA	NA	NA	NA
No symptoms	NA	10 (4.2)	NA	NA	NA

Data are presented as n or n (%), unless otherwise stated. NA: not available.

In these patients, in the presence of confirmed localised bronchiectasis, the operation is usually recommended independently on the severity of the haemoptysis, because delaying the operation may expose the patient to the risk of a sudden, massive, sometimes life threatening, haemoptysis. As presented in table 2, although the formation of an abscess represents an indication of the need to operate in approximately 10% of the patients studied, only 1% of the patients operated on in the series by Fujimoto *et al.* [5] underwent the surgery after being previously treated for pleural empyema caused by abscending bronchiectasis.

Although CF is, in general, not an indicator for thoracic surgery, according to some reports, *e.g.* Darlymple-Hay *et al.* [20], a small proportion of CF patients can develop severe localised bronchiectasis. As lung transplantation is not justified in this situation, encouraging results have been reported in a limited number of patients.

However, wherever possible, thoracic surgery should always be avoided in CF patients with embolisation as the first point of treatment for haemoptysis. Thus, where possible, these patients, before undergoing thoracic surgery, should be transferred to centres with extensive experience in the interventional management of severe, CF-related complications and lung transplantation.

Traditionally, based on morphology, bronchiectasis was classified into three variations: cylindrical, saccular and varicose. This classification is still widely accepted and the main criterion for resection is the response to medical treatment. However, since it was proposed, by Al-Kattan *et al.* [21], to classify bronchiectasis into perfused (usually cylindrical) and nonperfused (usually cystic), a new therapeutic approach has emerged, favouring the need for operations to only occur on patients with nonperfused bronchiectasis. Such an attitude was based on the fact that perfused bronchiectasis still retains the ability for gas exchange.

Although reasonable, this approach was not widely accepted, because, according to many reports, in most patients undergoing lung resection for bronchiectasis the respiratory function is not impaired. In one series of 125 patients who had undergone an operation, pre-operative forced expiratory volume in 1 s (FEV_1) was >60% predicted in 89.4% of patients, pre-operative vital capacity (VC) was >70% predicted in 80.8% of patients, whilst the diffusion capacity for the lung for carbon monoxide (D_{LCO}) was <70% in only 14.6% of patients. In the series by Prieto *et al.* [10] on 119 patients, the post-operative change in VC was 91% *versus* 89%, whilst the mean value for FEV_1 dropped from 83% to 81%. Such a pattern of post-operative lung function change is caused by a smaller lung volume of the lobe with bronchiectasis (compared with the lung volume of the unaffected lobe), thus contributing little to the ventilatory function (fig. 2).

The results of a recent report on 35 patients, by Giovannetti *et al.* [22], which showed that a mean±SD late, post-operative FEV_1 may be significantly lower than the pre-operative FEV_1 (89.9±16.3% *versus* 80.9±16.9%; p=0.0001), should be accepted with caution. In fact, of the 35 patients, 11 had an unchanged FEV_1 value, 15 had a limited FEV_1 loss (<15%), and nine had a

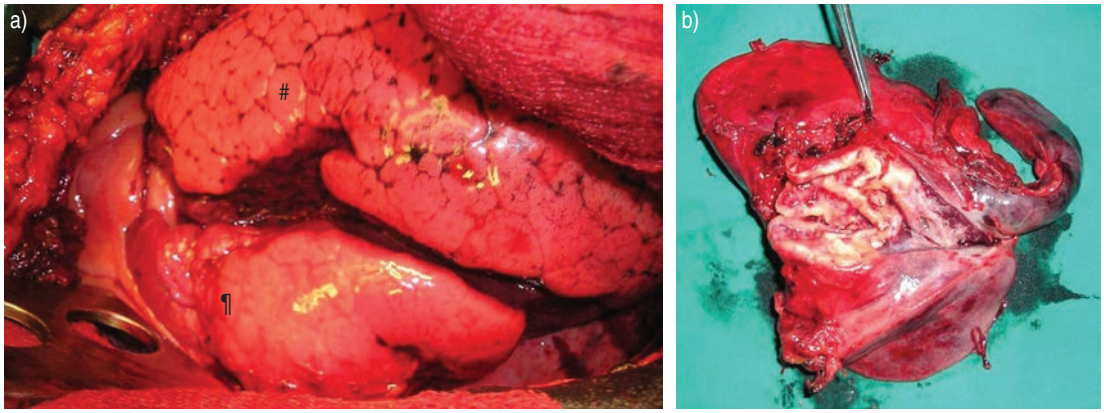


Figure 2. Lobe of the lung affected by bronchiectasis. a) Operating view of the lung. #: normal macroscopic aspect of the healthy, upper lobe; ¶: small-volume, left lower lobe affected by bronchiectasis. b) Operative specimen (lobectomy with a partial resection of the lingula), showing bronchiectatic area with condensation of the adjacent lung zones.

more important functional loss (an FEV_1 lowering >15%). Furthermore, a possible explanation for the result observed in this series, is that 11 of the patients with contra-lateral foci of bronchiectasis had more than just nonfunctional parenchyma removed, due to anatomical reasons.

Perfusion pattern

An example of perfusion pattern in nonperfused bronchiectasis is presented in figure 3. As presented, the left lower lobe is nearly nonperfused from the branches of the pulmonary artery, but a retrograde flow from the bronchial arterial system is evident. Sometimes, angiographic aspects of the absence of perfusion, through the pulmonary artery, may be the reflection of the dominant stream, through anastomotic bronchial arterial branches, in the opposite direction, thus preventing the contrast medium in the pulmonary artery to reach the lung periphery.

The value of modern CT angiography equals that of the standard procedure, so that today it is much more widespread than conventional angiography for the surgical evaluation of bronchiectasis in most centres.

The existence of anastomotic channels between bronchial circulation and peripheral branches of the pulmonary artery, in case of localised bronchiectasis, does not cause major haemodynamic consequences. But, in the more diffuse distribution of bronchiectasis cases, owing to the drainage of flow through the bronchial veins to the left heart, it may cause the left-heart embarrassment. Similarly, the described dominant retrograde stream within major pulmonary arteries, in case of diffuse distribution, may cause the right heart embarrassment as well.

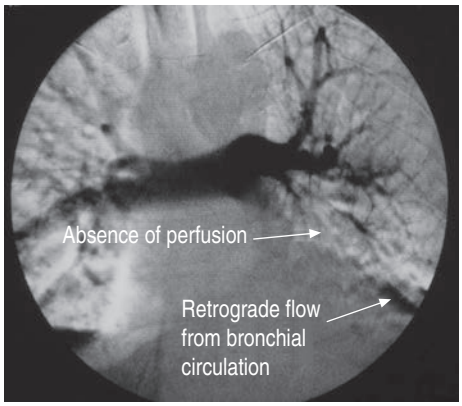


Figure 3. Perfusion pattern of left lower-lobe bronchiectasis.

An example of a better perfused bronchiectasis is presented in figure 4. In these patients, as the volume of the affected lobe may be similar to the non-affected lobe, the affected zone may not always be visible on standard posterior-anterior radiography. That is why, in the presence of typical symptoms, the lateral radiography should always be done, even in the absence of abnormalities on standard posterior-anterior radiography, otherwise bronchiectasis may be unforeseen.

The presence of bronchiectasis must be confirmed by CT scan. As presented on the removed specimen, despite a well preserved perfusion and macroscopically well preserved lobe, the affected zone is clearly damaged, representing the source of recurrent infections.

In brief, although a perfusion pattern is not a basic element for the indication to operate, the awareness of such a possible existence of different perfusion types, may help improve the understanding of this anastomotic blood-flow role in the possible genesis of both right- and left-heart embarrassment, in patients with bronchiectasis involving several lung zones.

Extent of the lung resection

Concerning the extent of resection, as presented on table 3, lobectomy is the most frequently performed procedure. It is sometimes combined with a limited resection of the affected part of the

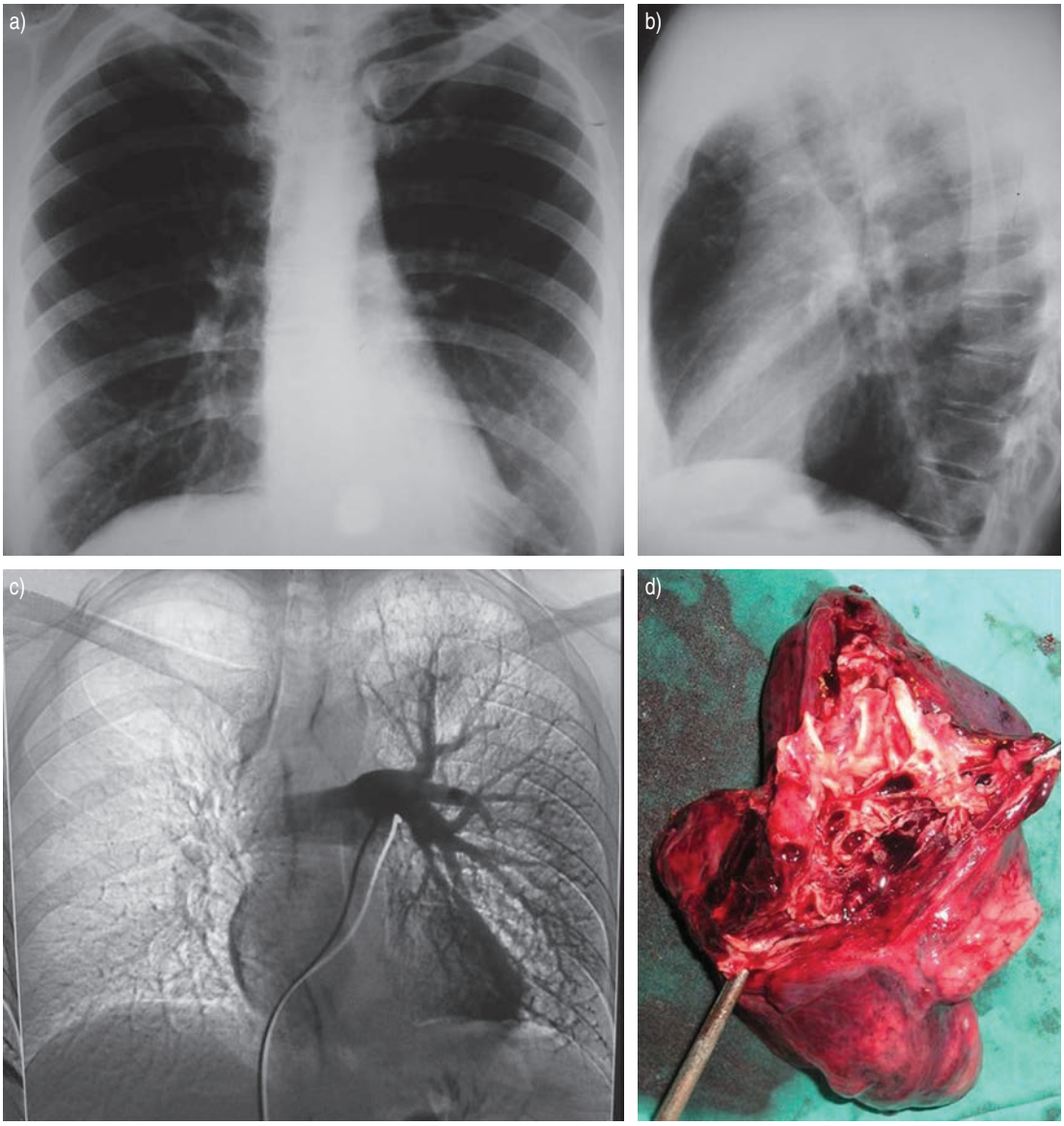


Figure 4. Perfused bronchiectasis. a) Posterior-anterior radiography, showing no major abnormalities. b) Lateral view of the left lower-lobe condensation. c) Pneumo-angiograph preserved perfusion of the affected left lower lobe. d) Operative specimen from a lobectomy.

adjacent lobe. Segmental resection is also justified, whenever possible, in order to spare the lung parenchyma. Anatomical lingular resection is a frequent choice. Preservation of the VI segment (the upper segment of the lower lobe) is sometimes possible in patients with basal segmentectomy and may not be associated with increased morbidity, as previously reported [23, 24].

A pneumonectomy is indicated for a small number of patients with a destroyed lung.

Usual clinical problems

In patients undergoing surgery for bronchiectasis, usual clinical problems are bilateral bronchiectasis, haemoptysis and previous pleural empyema.

Bilateral bronchiectasis

Traditionally, bilateral disease was for years a contraindication for lung resection. Recently, some surgeons have suggested that bilateral bronchiectasis is not always a contraindication for resection, but such an attitude is not widely accepted, with prolonged conservative treatment or bronchial arteries embolisation as alternatives. Literature data for surgical series with bilateral disease are scarce. In a series by PRIETO *et al.* [10], only two (20%) out of 10 patients with bilateral bronchiectasis were operated on. Similar percentages for operative treatment were reported by ASHOUR *et al.* [12] (18 (21%) out of 85 patients) and SCHNEITER *et al.* [25] (six (26%) out of 23 patients). MAZIERES *et al.* [26] reported five (31.2%) out of 16 patients were operated on for bilateral disease and in all those patients the number of resected segments was less than number of segments considered pathologic from the HRCT scan. In another series, by BALKANLI *et al.* [13], staged bilateral operation was done in 14 (45.1%) out of 31 patients with bilateral bronchiectasis.

Surgical resection in bilateral bronchiectasis should only be considered if medical therapies, consisting of: daily physical therapy; inhaled bronchodilators, which adequately address the extent of the bronchial obstruction; mucolytics, which include inhaled hypertonic saline; ''novel'' inhaled antibiotics; and anti-inflammatory treatment with macrolides, have all been unsuccessful.

There is still no consensus as to whether the more- or less-affected side should be operated upon first. The attitudes vary from the most dominant approach, where the more severely affected side is operated upon first, to an acceptance to operate first on the less affected side, through to a simultaneous or staged bilateral thoracotomy.

Suggestions that, in the case of bilateral disease, only nonperfused bronchiectasis should be operated upon, is not widely accepted. In his series, FUJIMOTO *et al.* [5] demonstrated that one in three of their patients, who had been operated upon, had cylindrical bronchiectasis (perfused) that had resulted in medically resistant symptoms, which were successfully alleviated by the operation.

Haemoptysis

Haemoptysis occurs in 56–92% of patients with bronchiectasis. Haemoptysis is more commonly observed in dry bronchiectasis, a rare disease variant (usually due to TB and localised in the upper lobes), with cough, but only minimal sputum production.

Haemoptysis is generally mild and manifests as blood spots in the patient's usual purulent sputum. This is often the factor that leads patients to consult a physician. Bleeding usually originates from dilated bronchial arteries, which contain blood at systemic (rather than pulmonary) pressures. Therefore, massive haemoptysis may occur, but is rarely a cause of death [27–29].

The literature from the 1940s through to the 1960s supports three major aetiologies for mass bleeding, which account for 90% of all cases, these are TB, bronchiectasis, and a lung abscess. Two modern studies of predominantly non-massive haemoptysis demonstrated that TB and bronchiectasis presently account for fewer cases of haemoptysis than in the past. The percentage

of bronchiectasis causing a massive haemoptysis decreased from 51% from a report in Stellenbosch, South Africa (1983–1990) [30], to 25% in a report from New York city, NY, USA (1991–1992) [31], through to 20% in a report from Jerusalem, Israel (1980–1995) [32].

Even in patients where bronchiectasis is the cause of haemoptysis, chest radiography may be not suggestive of bronchiectasis. In a series of 67 patients where haemoptysis was caused by bronchiectasis, although some radiographic abnormalities existed in 54% of patients, the diagnosis of bronchiectasis was only confirmed by chest radiography in 19% of the patients. However, bleeding was identified in 38 (56%) patients using bronchoscopy, with the upper lobe being predominant [33].

In patients with severe haemoptysis, embolisation of the bronchial arteries should be done wherever possible, not always to avoid resection, but to postpone it until the patient's general condition improves and an accurate assessment of the optimal extent of the resection becomes possible.

It is better to stabilise the patient first with an embolistion, if possible, before performing surgery to prevent further haemoptysis. Those unfit for pulmonary resection may require multiple courses of embolisation.

Experience of 50 patients with life-threatening haemoptysis, of which 46 underwent a bronchial-arterial embolisation, showed that in patients with a bleeding recurrence within 1 week of the initial embolisation, had bleeding from additional vessels, as well as some previously embolised vessels [34]. Angiography in hypotensive patients may cause a reduced flow or vasospasm, leading to cessation of bleeding in some vessels that may subsequently resume bleeding when the patient's haemodynamic status improves.

Although surgery is still a definitive treatment, emergency operations in patients who are unstable with bronchiectasis and on-going life-threatening haemoptysis are certainly associated with poor outcome (37% mortality) [30, 35].

A retrospective study comparing the outcome of bronchial arterial embolisation in 30 TB patients, 19 of which were bronchiectasis patients, showed that the haemoptysis recurrence rate was higher in chronic TB than in bronchiectasis; this was found to be related to incomplete feeding vessel embolisation [36].

If, for any reason, embolisation is not possible, different techniques may be used. For example fibrin glue can be applied directly through the fiberscope. Some modern bronchial blockers can be placed, under bronchoscopic guidance, through the endotracheal tube. In the absence of these modern devices a Fogarty catheter, previously manually curved, can be used as an alternative and can be positioned using bronchoscopic control.

Imaging procedures in a phase of active bleeding can be misleading in terms of the optimal extent of resection.

Table 3. Extent of the lung resection

First author [ref.]	Year	Patients	Less than a lobectomy	Lobectomy	Bilobectomy	Pneumonectomy	Lobectomy + segmental resection
FUJIMOTO [5]	2001	92	31 (33.7)	50 (54.3)	5 (5.4)	6 (6.5)	NA
BALKANLI [13]	2003	238	5 (2.1)	189 (79.4)	NA	13 (5.4)	31 (13)
KUTLAY [9]	2001	166	20 (12.2)	116 (69.8)	NA	13 (7.5)	17 (10.5)
PRIETO [10]	2001	119	15 (13)	74 (62)	4 (3)	10 (8)	16 (14)
AGASTHIAN [1]	1996	134	18 (13.4)	86 (64.2)	NA	21 (15.7)	9 (6.7)

Data are presented as n or n (%), unless otherwise stated. NA: not available.

In patients with haemoptysis, the clinical course and radiographic evolution may cause some confusion (fig. 5). After the massive haemoptysis has stopped, the retained coagulum may cause a complete lung atelectasis (fig. 5a). It is of importance to note here that one needs to be very careful when presented with gradually improving (fig. 5b), and finally a normal, radiographic aspect following a bronchoscopic aspiration of the coagulum in a patient without known bronchiectasis (fig. 5c). In this situation, a CT scan is always required, and can sometimes reveal localised bronchiectasis (fig. 5d). The operative aspect, showing hypotrophy of the lower lobe affected by bronchiectasis and specimen removed from the patient, are shown in figure 6.

Abscending bronchiectasis causing pleural empyema

In patients with abscending bronchiectasis, pleural empyema may precede the diagnosis of bronchiectasis, or represent a complication of known pre-existing bronchiectasis.

A particularly challenging situation exits if the operation is planned after the patient has been treated for pleural empyema in the presence of undetermined lung masses, as presented in figure 7. In fact, although the most important thing in this situation is to rule out lung cancer, intra-operatively the possibility of bronchiectasis should also be kept in mind. Bronchiectasis is confirmed post-operatively. As can be seen in the specimen removed, macroscopic aspects may be very similar to lung cancer, and also to organising pneumonia.

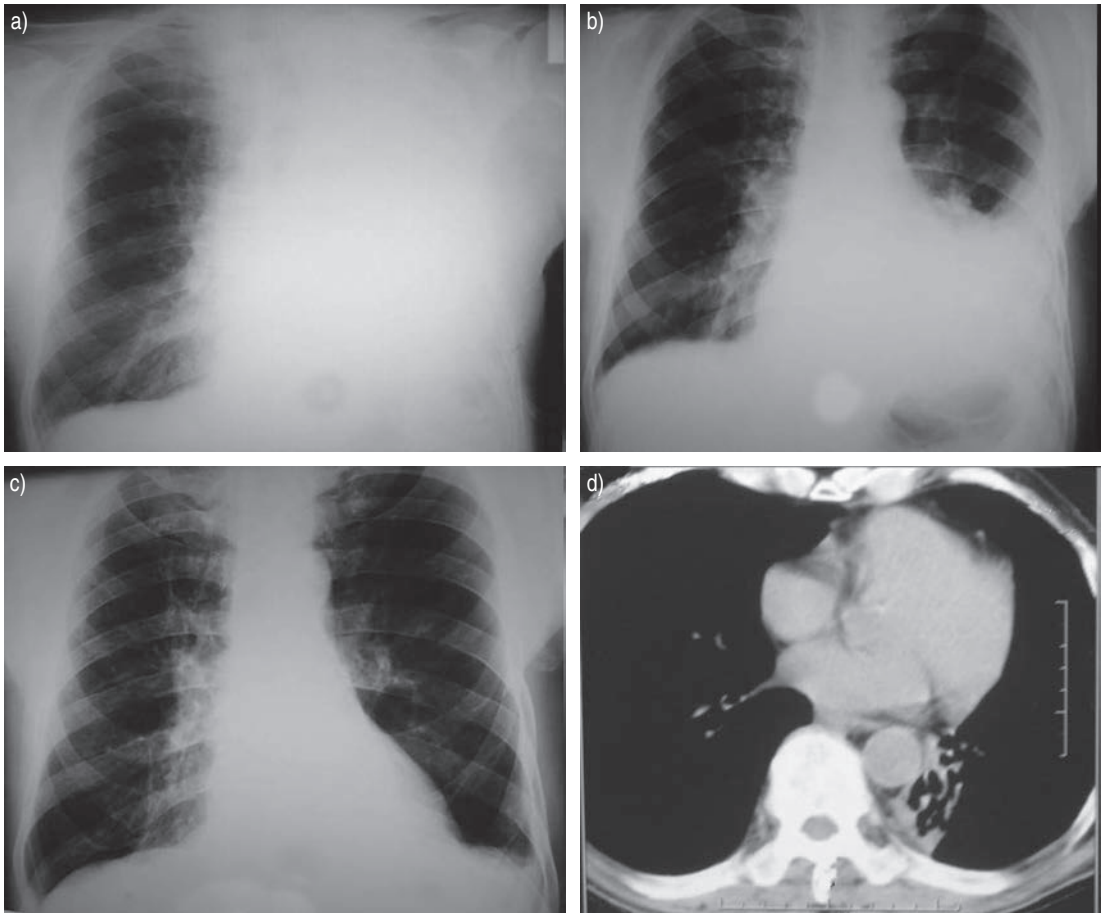


Figure 5. Bronchiectasis, which caused a major haemoptysis in a patient. a) Radiographic image of the lung upon patient admission. b) Radiographic image showing improvement after the first bronchoscopic aspiration. c) The radiographic aspect after repeated aspiration. d) A computed tomography image of a left lower-lobe bronchiectasis.

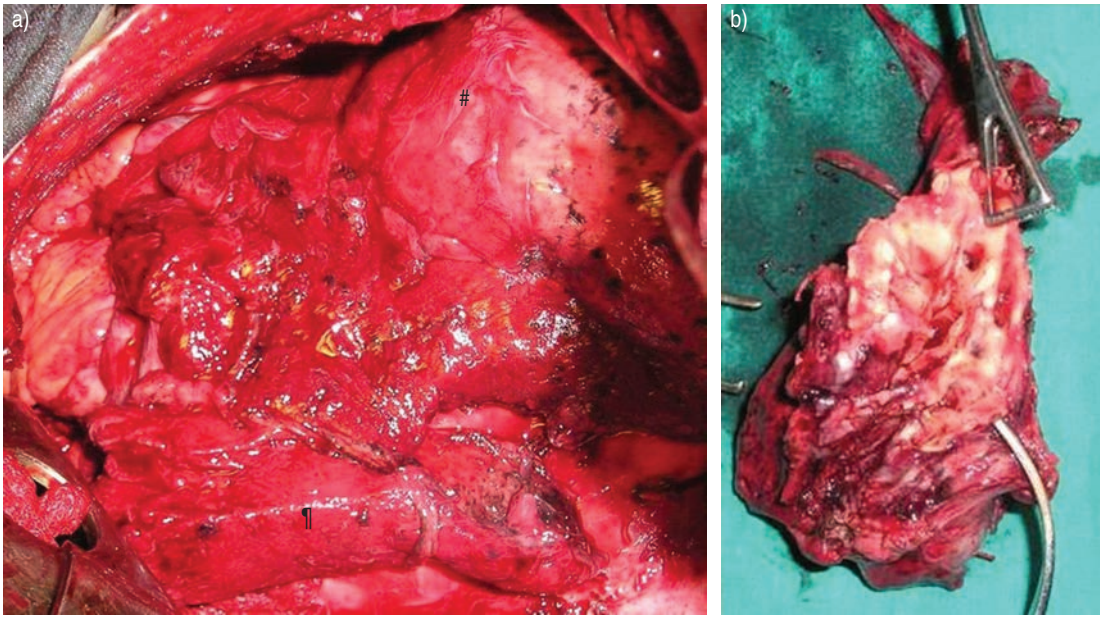


Figure 6. Bronchiectasis, which caused a major haemoptysis in the same patient as referred to in figure 5. a) The operative view. #: non-affected, upper lobe; ¶: the size of the affected left lower lobe is smaller. b) The specimen taken during the lobectomy.

Destroyed lung

In patients with the lung destroyed by bronchiectasis, pneumonectomy is the only surgical solution. Sometimes, a standard pneumonectomy is possible without major extrapleural liberation, despite bronchiectasis occupying the entire lung. If pleuropneumonectomy is anticipated from a CT scan, an intrapericardial approach to the lung vessels is usually necessary (fig. 8).

Apart from pneumonectomy performed for destroyed lung as an initial operation, completion pneumonectomy was also reported after previous surgery for bronchiectasis. In one recent report of a single-centre experience with this procedure over a 15-year period, found that 15 out of 23 patients, who underwent a completion pneumonectomy, had recurrent infections as the indicator

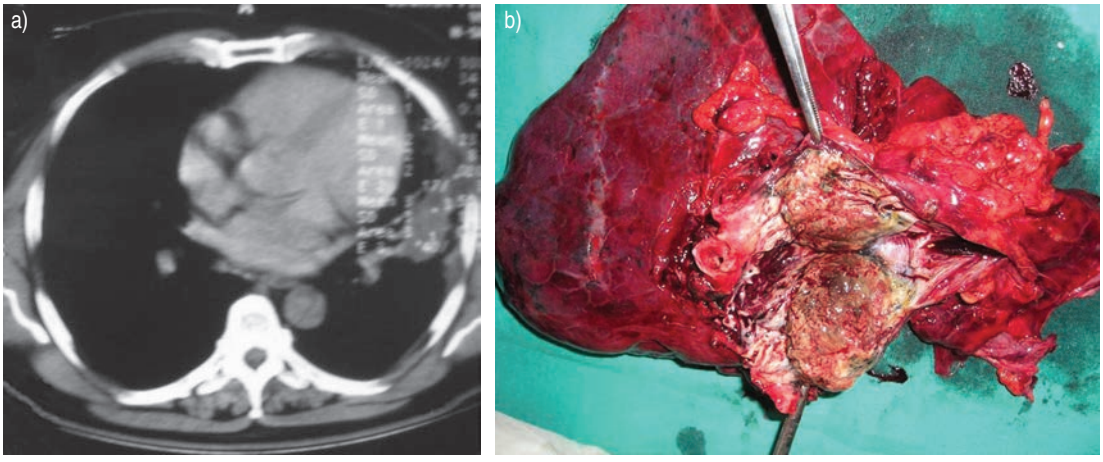


Figure 7. Lung resection for bronchiectasis, after previous pleural empyema. a) A computed tomography image showing persisting, undetermined, lung mass after the healing empyema. b) The operative specimen from a lobectomy showing a bronchiectatic area with a tumour-like aspect.

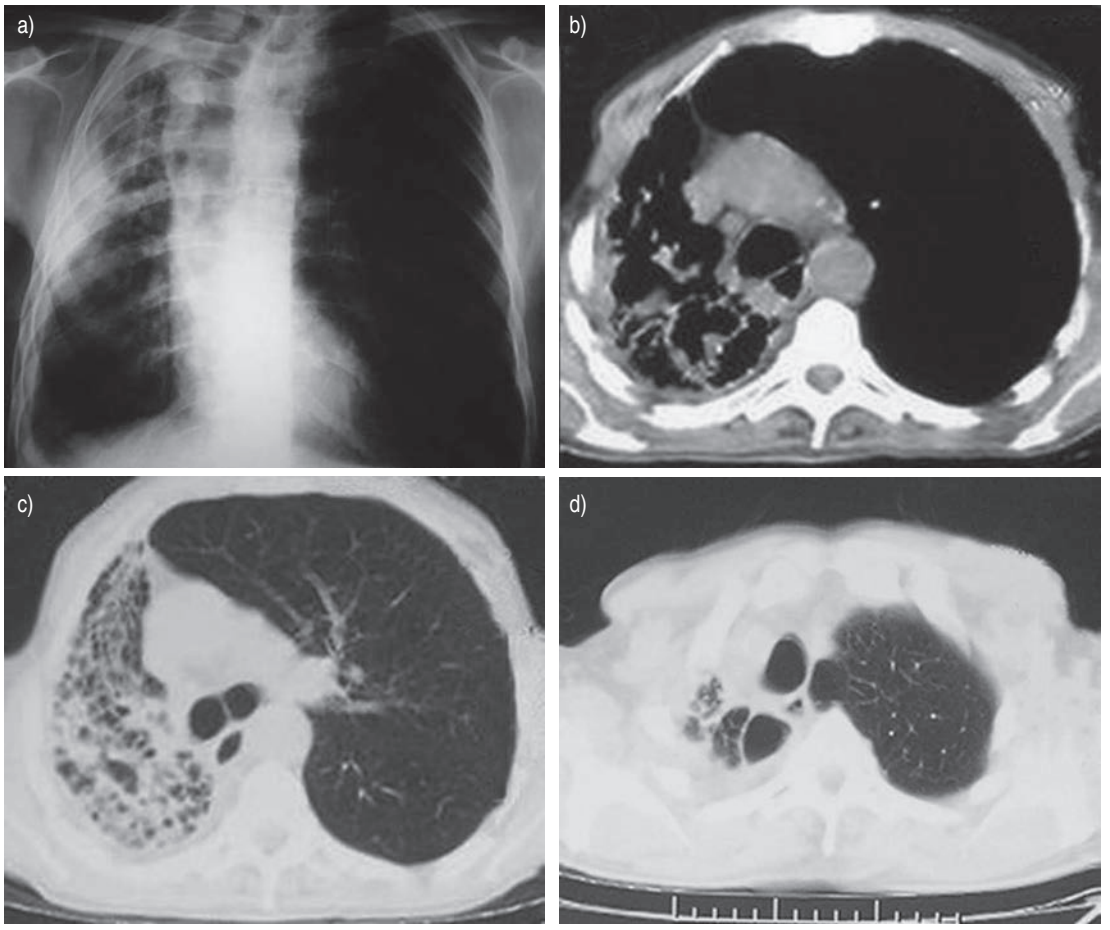


Figure 8. Bronchiectasis that has destroyed the lung. a) Posterior-anterior radiography. b–d) Computed tomotraphy scans, b) without contrast, at the level of the distal third of the trachea, c) with contrast, at the level of the tracheal bifurcation, and d) with contrast, at the level of the median part of the upper lobe.

for surgery [37]. The mean (range) time between the first operation and a complete pneumonectomy was 4.9 years (5 months–11 years). The mortality rate for 14 left- and nine right-complete pneumonectomies was 0, with a 43.5% operative morbidity (complications occurring within 30 days after surgery).

Although rarely, a unilaterally destroyed lung may be associated with pulmonary hypertension, due to systemic blood flow through bronchopulmonary shunts. In one reported series, which included four patients with a destroyed lung and pulmonary hypertension (mean pulmonary arterial pressure >25 mmHg) that had been treated by a pneumonectomy, two of the patients were found to have bronchiectasis as the underlying disease [38].

Bronchiectasis in children

Indications for surgical treatment are still not fully established in children. Criteria are roughly the same as for adults, taking into account the eventual presence of growth retardation or inability to follow the educational programme. The situation is more favourable in children with localised bronchiectasis, while diffuse bronchiectasis affection on multiple lobes or segments represents a more serious clinical problem.

The incidence of bronchiectasis in children varies between populations. For example, in New Zealand bronchiectasis was reported to exist in 3.7 per 100 000 children, whilst only 1% of 4000

children with respiratory symptoms had bronchiectasis unrelated to CF, according to data published in 1994 [39]. This rate is seven times higher than the only other comparable national study, which was 0.49 per 100 000 Finnish children aged <15 years, and equates to one in 1700 births being diagnosed with bronchiectasis before the age of 15 (approximately twice the rate of CF diagnosis, *i.e.* one per 3179) [40]. The limitation of population studies conducted years ago is the fact that HRCT was not used at the time, so the true incidence remains an unknown [41].

From a clinical standpoint, it should be noted that the diagnosis of bronchiectasis in children should be undertaken with great caution, as the bronchodilation can be reversible. Hence, it has been suggested that a diagnosis of established bronchiectasis in children, may only be justified if a combination of persistent clinical signs, and a persistent change on repeated CT examination, exists. The repeated evaluation by CT scans should be performed up to 2 years after the first scan, in a stable, clinical condition, and without signs of an acute infection [42].

Bronchiectasis in children has some specificity, which may influence the diagnostics and treatment. According to most clinical studies, the onset of symptoms in bronchiectasis patients occurred in the preschool years [43], with the most common symptoms being cough and sputum production [44]. Wheezing, reported in around 20% of bronchiectatic children may be the presenting symptom in as much as nearly half of the patients in some series [45]. Unlike in adults, haemoptysis is relatively uncommon in children, not exceeding 10% in some series [46]. Finger clubbing was reported in 3–51% of the bronchiectasis patients (for both adults and children).

All children with bronchiectasis should be investigated for an underlying cause, but the underlying aetiology may remain unidentified in up to 40% of patients. In a series of 111 patients, the mean $\pm$ SD age was 7.4 $\pm$ 3.7 years, the underlying aetiology was identified in 62.2% of the patients with the predominance of post-infectious bronchiectasis, existing in 29.7% [47]. Careful examination is necessary to confirm or exclude immunodeficiency, primary ciliary dyskinesia, asthma, and/or foreign-body aspiration.

The identification of an immunodeficiency in these patients is important, since they may benefit from an *i.v.* immunoglobulin (Ig) substitution. HILL *et al.* [48] reported that 6.6% of bronchiectatic patients had low IgG subclass values. Measurements of IgG subclass levels should be performed even if total IgG levels are found to be normal. It was recently shown that some patients with idiopathic bronchiectasis carried a mutation in the *ENaC* β or γ genes, giving a defective epithelial sodium channel (ENaC) protein [49].

Related to ciliary dyskinesia (Kartagener syndrome in the presence of situs inversus) abnormal ciliary motion leads to recurrent infections, due to the retention of secretions. The assessment of the ciliary ultrastructure is necessary to diagnose primary ciliary dyskinesia in these children. It was also reported that primary ciliary dyskinesia may be discovered on the basis of their low ciliary-beat frequency, even in several patients whose ciliary ultrastructure was normal [50]. Combined analysis of ciliary-beat frequency, beat pattern and ultrastructure might help to identify patients with primary ciliary dyskinesia in the group with unidentified underlying aetiology. According to British guidelines, ciliary investigations should be considered in children with bronchiectasis, if no other cause for bronchiectasis was identified; in patients with a history of chronic rhinitis, since the neonatal period or of neonatal respiratory distress; and in patients with dextrocardia [51].

An important practical question is: which children should be investigated for bronchiectasis? Apart from children with recurrent pneumonia or unexplained haemoptysis, the existence of bronchiectasis should be considered in children with: chronic productive cough; asthma and not responding to treatment; or with pertussis (whooping cough)-like symptoms that are not resolved after 6 months. Furthermore, respiratory symptoms in children with structural or functional disorders of the oesophagus may also be suggestive of bronchiectasis.

Surgical treatment is performed in children with clearly decreasing frequency, mostly due to early diagnosis and improved medical treatment [52]. However, there are no clear recommendations

related to the optimal duration of medical treatment before surgery. In the presence of localised disease, segmental or lobar resection is indicated [9]. The reported rate of surgically-treated patients with bronchiectasis is around a quarter; however, a certain time-trend with a tendency of decreased need for surgery, in the more recent period, was noticed (40% *versus* 15%, respectively), even within the same patient series, if the analysed period is 15 years [37].

Concerning the outcome of treatment, according to the classical study by WILSON and DECKER [53], significant improvement exists in 75% of patients who are operated on, 22% are improved and remain 4% unchanged, compared with 69% of unchanged and 23% deteriorated patients, respectively, in the nonsurgical group.

Results for the surgical treatment of bronchiectasis

The outcome of surgical treatment is good, according to most early- and recently reported series, as presented in tables 4 and 5 [1, 5, 9, 12–14, 43, 54–58], with low operative mortality and morbidity, but higher than reported for noninfectious pathology.

Complications of surgery usually range between 10% and 25%, and mostly consist of prolonged air leak, bleeding, empyema, and/or respiratory failure. In most series, a lobectomy is the most common type of resection, with a rate of approximately 60%.

Role of VATS in patients with bronchiectasis

Video-assisted thoracoscopic surgery (VATS) pulmonary resection has become an established alternative approach to conventional open surgery for selected patients [59, 60]. Due to the continuous development of the minimal invasive surgical techniques, VATS has become for major lung resections, such as segmentectomies and lobectomies, a more frequent procedure in experienced centres. VATS offers many potential advantages over open surgery, including less post-operative pain, improved cosmetic outcomes, better preservation of pulmonary function in the early post-operative period, an earlier return to full activities, and a better quality of life after recovery [25].

In patients with localised bronchiectasis, VATS may be seen as an option in the presence of marked symptoms and with the extension of the disease requiring either nonanatomical or anatomical resection, such as a lobectomy.

Furthermore, VATS may be indicated in elderly patients, who may benefit from the advantages of a minimally invasive procedure, or in younger patients, who request better cosmetic outcomes [58].

Table 4. The outcome of surgical treatment for bronchiectasis before 2001

First author [ref.]	Period of study years	Patients n	Outcome			Operation	
			Excellent	Improved	Not improved	Morbidity	Mortality
SANDERSON [54]	1952–1967	242	150 (62)	58 (24)	34 (14)	33	0.4
WILSON [43]	1964–1980	84	63 (75)	18 (21)	3 (4)	11	0
MANDARIC [14]	1972–1978	145	129 (89)	6 (4)	10 (7)	38	2
AGASTHIAN [1]	1976–1993	134	79 (59)	39 (29)	16 (12)	25	2.2
ASHOUR [12]	1987–1997	85	63 (74)	19 (22)	3 (3.5)	17	0
PRIETO [10]	1988–1999	119	80 (67.6)	34 (29)	5 (4)	15	0
FUJIMOTO [5]	1990–1997	92	42 (46)	35 (38)	15 (16)	20	0
BALKANLI [13]	1992–2001	238	189 (79.4)	28 (12)	11 (4.6)	8.8	0
KUTLAY [9]	1990–2000	166	140 (84.7)	23 (13.8)	3 (1.5)	11	1.7

Data are presented as n (%) or %, unless otherwise stated.

In patients with localised bilateral disease, this minimally invasive technique may enable surgery to be undertaken on both sides in the same theatre session. In these patients quantitative perfusion scintigraphy (SPECT)-CT might be useful, especially when pulmonary function is poor [61].

Table 5. The outcome of surgical treatment for bronchiectasis post 2001

First author [ref.]	Publication year	Patients n	Operation	
			Morbidity	Mortality
ZHANG [55]	2010	790	128 (16.2)	0
EREN [56]	2007	143	33 (23)	1.3
HIRAMATSU [57]	2012	31	6 (18)	0
ZHANG [58]	2011	52	14 (26.95)	0

Data are presented as n (%) or %, unless otherwise stated.

Based on the several advantages of the minimally invasive surgery, the VATS technique may be used earlier in patients without marked symptoms, thereby preventing the extension of the disease to other parts of the lungs and the need for major resections associated with more complications.

Conditions required for VATS resection in patients with bronchiectasis are: 1) a centre with major experience in VATS surgery; 2) no severe parenchymal and/or pleural scarring; and 3) no calcified lymph nodes near pulmonary arteries or veins shown on a CT-scan [58].

The entire VATS procedure is performed without rib spreading. Patients are placed in the lateral decubitus position and one lung-ventilation is established through a double-lumen endotracheal tube. The first 10 mm trocar is placed. The camera, usually with a 30° lens, is introduced. The cavity is carefully explored and the feasibility of a VATS procedure assessed. If the procedure is completely performed endoscopically the operating trocars (10 mm and 5 mm) are inserted into intercostal spaces, depending on the localisation of the bronchiectasis. The hilar dissection is done as in an open lobectomy. This includes the individual isolation of vessels and bronchus. Major pulmonary arteries and veins are usually transacted, by the use of endoscopic stapling devices.

At the end of the procedure, the resected part of the lung is stored in a specimen bag and taken out from the hemithorax to prevent contamination and empyema or wound infection. In the case of a lobectomy, a minithoracotomy is performed at the end of the procedure to remove the specimen. A small utility thoracotomy can be also performed at the beginning of the operation. In this case combinations of conventional and endoscopic instruments are used for dissection, but rib spreading is never inserted. This approach is particularly useful when inflammatory changes are marked, which can make dissection more difficult.

For bilateral well-localised bronchiectasis, single-stage bilateral-sequential thoracoscopy can be used, which is an advantage in comparison with two-stage bilateral open surgery.

For VATS resections, epidural catheter is not routinely indicated. An indication consists of situations in which conversion to open surgery is probable.

The number of studies dealing with VATS for the treatment of bronchiectasis is limited. There are no prospective studies comparing morbidity after open and minimal invasive surgery.

In the retrospective study by ZHANG *et al.* [58], they compared the outcome of 279 patients who underwent a thoracotomy and 52 patients who underwent a VATS procedure for bronchiectasis with epidural catheter for pain management. In all patients a lobectomy was performed, the follow-up time was 43 months. There was no difference in the blood loss and median operative time; however, the patients with VATS had a shorter length of stay in the hospital, fewer complications (17.5% *versus* 23.7%) and also suffered significantly less pain. 94% and 88 % of the patients fully recovered (complete absence of pre-operative symptoms) after the operation by VATS and thoracotomy, respectively. The authors concluded that a VATS lobectomy for localised bronchiectasis is a safe and more efficient procedure in selected patients with a better recovery. The most frequent complication consists of prolonged air leak [51].

The study by SCHNEITER *et al.* [25] showed that nonlocalised disease to one lobe should not be regarded as a general contraindication to surgery. Satisfaction with the outcome of an operation was the same in patients with localised disease in one lobe and patients with bronchiectasis affecting at least one segment in two different lobes, unilaterally or bilaterally. The proportion of patients whose condition was improved was comparable to other reports (60–90%). The VATS approach can be used early to prevent progressive destruction of the bronchial wall by recurrent infection and arrest the disease before it becomes more widespread.

VATS may play an important role in the treatment of bronchiectasis in experienced centres, familiar with the minimal invasive approach. The feasibility of resection using this technique also depends on the extension of adhesions and on the presence of large, calcified hilar-lymph nodes. VATS can lead to a complete resection of the disease, but potentially offers all the advantages of the minimal invasive technique in comparison to the open approach, particularly regarding post-operative pain and duration of hospitalisation. Nonlocalised and even bilateral lung involvement can be successfully treated by VATS in selected patients, yielding comparable overall results to those for patients with localised bronchiectasis. The advantage of VATS is the possibility to treat both sides in one session and to offer a potential cure for the disease in elderly patients or to prevent an extension of bronchiectasis.

Study limitations

The present review has several limitations that may influence the overall educational aim. First, most of the reported surgical series are of a retrospective nature in general, with only a few having been recently published. Secondly, the number of up-to-date studies in times of modern medical treatment options for bronchiectasis is still limited, so that the optimal timing for referral of these patients to surgery cannot be entirely evidence based. Finally, the limited number of studies on VATS in patients with bronchiectasis, does not allow firm conclusions to be made about the value of this procedure in this group of patients.

Conclusion

Surgical treatment of bronchiectasis comes into consideration either as an elective or urgent procedure.

Currently, diagnosis is based on HRCT, which is noninvasive and equally reliable, if not more so, than bronchography that was abandoned as a diagnostic tool more than 15 years ago. Furthermore, HRCT and SPECT give a much better insight into the perfusion pattern and the quality of the other lung zones.

In a great majority of patients surgery is recommended in patients with chronic, repeated infections whose normal life is disturbed by the need for frequent hospitalisations and excessive medications.

The widespread belief that surgery is justified only for unilateral bronchiectasis has been challenged by several reports, which have demonstrated that staged bilateral approach with parenchyma-sparing resections (by thoracotomy or VATS) may also be appropriate from the standpoint of the treatment outcome. However, surgical resection in bilateral bronchiectasis should only be considered if medical therapy was unsuccessful.

VATS may be indicated in elderly patients, who may benefit from the advantages of a minimal-invasive procedure, or in younger patients, who request better cosmetic outcomes. Whether the VATS technique may be used earlier in patients without marked symptoms to avoid extension of the disease in other parts of the lungs, and also major resection, is still not evidence based.

According to all reported surgical series, the treatment outcome after surgery for localised form of bronchiectasis is good from the standpoint of the symptoms relief and recurrence prevention.

Statement of Interest

None declared.

References

1. Agasthian T, Deschamps C, Trastek VF, *et al.* Surgical management of bronchiectasis. *Ann Thorac Surg* 1996; 62: 976–980.
2. Weycker D, Edelsberg J, Oster G, *et al.* Prevalence and economic burden of bronchiectasis. *Clin Pulm Med* 2005; 12: 205–209.
3. Seitz AE, Olivier KN, Steiner CA, *et al.* Trends and burden of bronchiectasis-associated hospitalisations in the United States, 1993–2006. *Chest* 2010; 138: 944–949.
4. Seitz AE, Olivier KN, Adjemian J, *et al.* Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. *Chest* 2012; 142: 432–439.
5. Fujimoto T, Hillejan L, Stamatis G. Current strategy for surgical management of bronchiectasis. *Ann Thorac Surg* 2001; 72: 1711–1715.
6. King PT. The pathophysiology of bronchiectasis. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 411–419.
7. O'Brien C, Guest PJ, Hill SL, *et al.* Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635–642.
8. Patel IS, Vlahos I, Wilkinson TM, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.
9. Kutlay H, Cangir AK, Enon S, *et al.* Surgical treatment in bronchiectasis: analysis of 166 patients. *Eur J Cardiothorac Surg* 2002; 21: 634–637.
10. Prieto D, Bernardo J, Matos MJ, *et al.* Surgery for bronchiectasis. *Eur J Cardiothorac Surg* 2001; 20: 19–23.
11. Nicotra MB, Rivera M, Dale AM, *et al.* Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest* 1995; 108: 955–961.
12. Ashour M, Al-Kattan K, Rafay MA, *et al.* Current surgical therapy for bronchiectasis. *World J Surg* 1999; 23: 1096–1104.
13. Balkanli K, Genç O, Dakak M, *et al.* Surgical management of bronchiectasis: analysis and short-term results in 238 patients. *Eur J Cardiothorac Surg* 2003; 24: 699–702.
14. Mandaric D. Bronchiectasis – contemporary diagnostic and therapeutic procedures. PhD thesis; University of Belgrade, Belgrade, Serbia, 1983.
15. Young K, Aspestrand F, Kolbenstvedt A. High resolution CT and bronchography in the assessment of bronchiectasis. *Acta Radiol* 1991; 32: 439–441.
16. Suga K, Yasuhiko K, Iwanaga H, *et al.* Functional mechanism of lung mosaic CT attenuation: assessment with deep-inspiration breath-hold perfusion SPECT-CT fusion imaging and non-breath-hold Technegas SPECT. *Acta Radiol* 2009; 50: 34–41.
17. McGuinness G, Naidich DP. CT of airways disease and bronchiectasis. *Radiol Clin North Am* 2002; 40: 1–19.
18. Bruzzi JF, Rémy-Jardin M, Delhaye D, *et al.* Multi-detector row CT of hemoptysis. *Radiographics* 2006; 26: 3–22.
19. Kang EY, Miller RR, Müller NL. Bronchiectasis: comparison of preoperative thin-section CT and pathologic findings in resected specimens. *Radiology* 1995; 195: 649–654.
20. Dalrymple-Hay MJ, Lucas J, Connett G, *et al.* Lung resection for the treatment of severe localised bronchiectasis in cystic fibrosis patients. *Acta Chir Hung* 1999; 38: 23–25.
21. Al-Kattan KM, Essa MA, Hajjar WM, *et al.* Surgical results for bronchiectasis based on hemodynamic (functional and morphologic) classification. *J Thorac Cardiovasc Surg* 2005; 130: 1385–1390.
22. Giovannetti R, Alifano M, Stefani A, *et al.* Surgical treatment of bronchiectasis: early and long-term results. *Interact Cardiovasc Thorac Surg* 2008; 7: 609–612.
23. Collis JL. Fate of the lower apical segment in resections for bronchiectasis. *Thorax* 1953; 8: 323–325.
24. Hoffman E. The late results of the conservation of the apical segment of the lower lobe in resections for bronchiectasis. *Thorax* 1955; 10: 137–141.
25. Schneiter D, Meyer N, Lardinois D, *et al.* Surgery for non-localized bronchiectasis. *Br J Surg* 2005; 92: 856–859.
26. Mazières J, Murris M, Didier A, *et al.* Limited operation for severe multisegmental bilateral bronchiectasis. *Ann Thorac Surg* 2003; 75: 382–387.
27. Barker AF. Bronchiectasis. *N Engl J Med* 2002; 346: 1383–1393.
28. King PT, Holdsworth SR, Freezer NJ, *et al.* Characterisation of the onset and presenting clinical features of adult bronchiectasis. *Respir Med* 2006; 100: 2183–2189.
29. Flume PA, Yankaskas JR, Ebeling M, *et al.* Massive hemoptysis in cystic fibrosis. *Chest* 2005; 128: 729–738.
30. Knott-Craig CJ, Oostuizen JB, Rossowv G, *et al.* Management and prognosis of massive hemoptysis. Recent experience with 120 patients. *J Thorac Cardiovasc Surg* 1993; 105: 394–397.
31. McGuiness G, Beacher JR, Harkin TJ, *et al.* Hemoptysis: prospective high resolution CT/bronchoscopic correlation. *Chest* 1994; 105: 1155–1162.
32. Hirshberg B, Biran I, Glazer M, *et al.* Hemoptysis: etiology, evaluation and outcome in the tertiary referral hospital. *Chest* 1997; 112: 440–444.
33. Noriaki T, Miki Y, Kiyoko M, *et al.* Hemoptysis with bronchiectasis. *J Japan Soc Bronchol* 1999; 21: 11–15.

34. Yeong Phang L, Wong D, Agasthian T. Management of life threatening hemoptysis. *Asian Cardiovasc Thorac Ann* 2001; 9: 200–203.
35. Gourin A, Garzon AA. Operative treatment of massive hemoptysis. *Ann Thorac Surg* 1974; 18: 52–60.
36. Lee JH, Kwon SY, Yoon HI, *et al.* Haemoptysis due to chronic tuberculosis *vs.* bronchiectasis: comparison of long-term outcome of arterial embolisation. *Int J Tuberc Lung Dis* 2007; 11: 781–787.
37. Sirmali M, Karasu S, Gezer S, *et al.* Completion pneumonectomy for bronchiectasis: morbidity, mortality and management. *Thorac Cardiovasc Surg* 2008; 56: 221–225.
38. Tanaka H, Matsumura A, Okumura M, *et al.* Pneumonectomy for unilateral destroyed lung with pulmonary hypertension due to systemic blood flow through broncho-pulmonary shunts. *Eur J Cardiothorac Surg* 2005; 28: 389–393.
39. Nikolaizik WH, Warner JO. Aetiology of chronic suppurative lung disease. *Arch Dis Child* 1994; 70: 141–142.
40. Twiss J, Metcalfe R, Edwards E, *et al.* New Zealand national incidence of bronchiectasis "too high" for a developed country. *Arch Dis Child* 2005; 90: 737–740.
41. Pasteur MC, Bilton D, Hill AT. BTS guideline for non-CF bronchiectasis - a quick reference guide. British Thoracic Society Reports, Vol 2, No 2, 2010, London, British Thoracic Society.
42. Gaillard EA, Carty H, Heaf D, *et al.* Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. *Eur J Radiol* 2003; 47: 215–220.
43. Brown MA, Lemen RJ. Bronchiectasis. *In* Chernick V, Boat TF, Kendig EL eds. Kendig's Disorders of Respiratory Tract in Children 1998. Philadelphia, Saunders, pp. 538–552.
44. Lewinston NJ. Bronchiectasis. *In* Hilman BC, ed. Pediatric Respiratory Disease. 3rd Edn. Philadelphia, Saunders, 1993; pp 222–229.
45. Dagli E. Non-cystic fibrosis bronchiectasis. *Paediatr Respir Rev* 2000; 1: 64–70.
46. Ferkol TW, Davis PB. Bronchiectasis and bronchiolitis obliterans. *In* Taussig LM, Landau LI, Le Souëf PN, *et al.* eds. Pediatric Respiratory Medicine. St Louis, Mosby, 1999; pp. 784–789.
47. Karadag B, Karakoc F, Ersu R, *et al.* Non-cystic fibrosis bronchiectasis in children: a persisting problem in developing countries. *Respiration* 2005; 72: 233–238.
48. Hill SL, Mitchell JL, Burnett D, *et al.* IgG subclasses in the serum and sputum from patients with bronchiectasis. *Thorax* 1998; 53: 463–468.
49. Fajac I, Viel M, Sublemontier S, *et al.* Could a defective epithelial sodium channel lead to bronchiectasis. *Respir Res* 2008; 9: 46.
50. Buchdahl RM, Reiser J, Ingram D, *et al.* Ciliary abnormalities in respiratory disease. *Arch Dis Child* 1988; 63: 238–243.
51. Pasteur MC, Bilton D, Hill AT. BTS guideline for non-CF bronchiectasis. *Thorax* 2010; 65: Suppl. 1, i1–i58.
52. Singleton R, Morris A, Redding G, *et al.* Bronchiectasis in Alaska native children: causes and clinical courses. *Pediatr Pulmonol* 2000; 29: 182–187.
53. Wilson JF, Decker AM. The surgical management of childhood bronchiectasis. A review of 96 consecutive pulmonary resections in children with nontuberculous bronchiectasis. *Ann Surg* 1982; 195: 354–363.
54. Sanderson JM, Kennedy MC, Johnson MF, *et al.* Bronchiectasis: results of surgical and conservative management. A review of 393 cases. *Thorax* 1974; 29: 407–416.
55. Zhang P, Jiang G, Ding J, *et al.* Surgical treatment of bronchiectasis: a retrospective analysis of 790 patients. *Ann Thorac Surg* 2010; 90: 246–250.
56. Eren S, Esme H, Avci A. Risk factors affecting outcome and morbidity in the surgical management of bronchiectasis. *J Thorac Cardiovasc Surg* 2007; 134: 392–398.
57. Hiramatsu M, Shiraishi Y, Nakajima Y, *et al.* Risk factors that affect the surgical outcome in the management of focal bronchiectasis in a developed country. *Ann Thorac Surg* 2012; 93: 245–250.
58. Zhang P, Zhang F, Jiang S, *et al.* Video-assisted thoracic surgery for bronchiectasis. *Ann Thorac Surg* 2011; 91: 239–243.
59. Farjah F, wood DE, Mulligan MS. Safety and efficacy of video-assisted *versus* conventional lung resection for lung cancer. *J Thorac Cardiovasc Surg* 2009; 137: 1415–1421.
60. Yuncu G, Ceylan KC, Sevinc S. Resultados funcionales del tratamiento quirúrgico de las bronquiectasias en un país en vías de desarrollo. [Functional results of surgical treatment of bronchiectasis in a developing country.] *Arch Bronconeumol* 2006; 42: 183–188.
61. Donnelly LF, Gelfand MJ, Brody AS, *et al.* Comparison between morphologic changes seen on high-resolution CT and regional pulmonary perfusion seen on SPECT in patients with cystic fibrosis. *Pediatr Radiol* 1997; 27: 920–925.

Chapter 10

Hydatid disease of the lungs

Danail Petrov and Kalliopi Athanassiadi#*

SUMMARY: Pulmonary echinococcosis is the most severe form of helminthic zoonosis, which has significant medical, social and economical impact. Surgery is the primary mode of treatment. The diversity of the hydatid pathological process offers various treatment tactics and approaches (especially in the bilateral and associated forms), which must be individually tailored in each and every case. Organ-preserving extirpation techniques, by open surgery or video-assisted thoracoscopic surgery, are the methods of choice. Anatomical resections are justified only when a certain anatomical structure is completely destroyed by a giant cst or several uncomplicated cysts, as well as in complicated echinococcosis with irreversible changes in the adjacent lung parenchyma. The incidence rates of morbidity and mortality are low. Post-operative chemoprevention is indicated only in cases of intra-operative dissemination and suspicion of residual cysts. Chemotherapy alone is an alternative for patients with multiple, single intact cysts or relapses, and for those who can not tolerate surgery.

*Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases, Medical University, Sofia, Bulgaria.
#Dept of Thoracic Surgery, Evangelismos General Hospital, Athens, Greece.

Correspondence: D. Petrov, Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases, 19 Ivan Geshov Str., 1431 Sofia, Bulgaria.
Email: danail_petrov@hotmail.com

Eur Respir Monogr 2013; 61: 107–121.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041312
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Hydatid disease or echinococcosis is a parasitic infection, a disease that affects both humans and other mammals. It was first described in the works of Hippocrates in the 4th century AD. The forms of echinococcosis found in humans are caused by the larval stages of different species of the tapeworm of genus *Echinococcus*. The most common form is cystic echinococcosis (unilocular echinococcosis), which is caused by *Echinococcus granulosus*. This form has a worldwide distribution and is endemic in many countries in the Mediterranean region, the Middle and Far East, and South America [1]. The second is alveolar echinococcosis (multilocular echinococcosis), which is caused by *Echinococcus multilocularis* in the Northern hemisphere, including central Europe and the northern parts of Europe, Asia and North America. Other forms of echinococcosis, which are caused by *Echinococcus vogeli* and *Echinococcus oligarth*, are rare [2].

The adult *E. granulosus* is a worm that resides in the jejunum of dogs and other canines and produces eggs that are passed in the stool. Eggs ingested by intermediate hosts (cows, sheep, mice, caribou and humans) liberate an embryo in the duodenum, which passes through the intestinal mucosa to enter portal circulation. Most of these embryos are trapped in the liver; the rest pass through the liver and are scattered to other organs and develop into hydatid cysts. However, while less common, the lymphatic system or bronchi can also serve as the pathway for infestation [2]. Within the thorax, the lung is the organ most frequently colonised, especially the lower lobes [3]. If the hexacanth embryo manages to get past the pulmonary filter, it reaches the left heart and by

way of the aorta, and from there the remainder of the organism. A hydatid cyst develops from the embryo released from an egg; this grows from a few millimetres in size up to ~5 cm a year and is able to survive within organs for a long period of time [1, 2].

Pulmonary echinococcosis is the most severe form of helminthic zoonosis, and has significant medical, social and economical impact [4, 5].

Morphologically, the hydatid cyst consists of three layers and hydatid fluid. The first layer is the pericyst or adventitia, which is the host tissue formed by the lung as a reaction to the foreign body (parasite). The other two layers, the laminated membrane (the external layer of the cyst) and the germinative layer (the inner layer of the cyst), belong to the parasite. The cyst fluid resembles water in appearance, containing brood capsules and protoscolices. In some cases, daughter vesicles, formed by germinative membrane, may be found [1, 2].

The lungs have the second highest rate organ location of echinococcosis after the liver (20–35%) [1, 2, 6]. Due to the anatomical characteristics of lung parenchyma, pulmonary cysts grow more rapidly in comparison with the remaining locations, and they can achieve large dimensions [7]. The cysts are most frequently solitary; multiple echinococcosis is found in 10–40% of patients [8]. Bilateral localisation is observed in 10–20%; combined (associated) echinococcosis with other organ location (in most cases, the liver) is found in 4–21% [9–12]. Transdiaphragmatic migration of hydatid cysts from the posterior segments of the right hepatic lobe is reported to be a common complication and is probably related to their proximity to the diaphragm [13].

Intrathoracic extrapulmonary cysts are rare and their incidence rate varies between 4.5% and 6.7% [14, 15]. Within the chest, echinococcosis can primarily involve the pleural cavity, mediastinum, chest wall, diaphragm, pericardium, heart and pulmonary artery [14–17].

Clinical presentation

Uncomplicated hydatid cysts

Uncomplicated hydatid cysts are usually asymptomatic and they are discovered during radiography on an unrelated occasion. Symptoms are produced by two mechanisms: a generalised toxic reaction due to the presence of the parasite itself (headache, anorexia, fatigue and recurring urticaria rash) and local or mechanical symptoms depending on the location of the cyst. The mechanical symptoms also depend on the size and number of the cysts. The increase in the cyst size leads to compression of the neighbouring organs and structures with the appearance of chest heaviness and pain. Later on, dry cough or cough accompanied of scarce mucinous expectoration is added, scarce haemoptoe and additional general complaints might occur (such as general weakness, subfebrile temperature, chills, sweating, *etc.*). Shortness of breath and haemodynamic disorders accompany the very large cysts.

Complications

Evolution of the parasite may lead to various complications. Rupture, secondary infection and suppuration are the most common complications. They usually precede the diagnosis of the disease [18, 19].

Development of adventitia calcification due to the more rapid growth of pulmonary cysts is rare [7]. It is not a sign of parasitic death, although the two events may be combined [2].

Cyst suppuration without perforation develops after blood- or air-borne pathogenic micro-organisms enter the cyst. Cyst suppuration might also occur following diagnostic puncture, which is an error in art. Suppuration is manifested with aggravation of cough and expectoration, as well as with fever, sometimes of the septic type [9, 19].

Cyst perforation into the bronchial tree, occurring in 20–40% of cases, is the most frequent complication [3, 10]; this might occur spontaneously or it might be induced by trauma or physical effort, even bilaterally [20]. Larger pulmonary cyst rupture is more common [21]. Cyst perforation is manifested with expectoration of a large amount of clear salty-bitter in taste fluid, in which parasite elements might be found out (membranes, daughter cysts, *etc.*). The suppurated cysts perforate with vomique or more frequently with gradual expectoration of purulent-like and fetid matter. Haemoptoe is a sign of occurring perforation but it only rarely reaches the intensity of haemorrhage implying emergency surgery [2]. Spontaneous healing after an expectoration into a large bronchus as well as bronchogenic dissemination with the development of secondary echinococcosis are exceptionally rare [1]. The cavity formed after the perforation is usually infected and the disease course is of the character of secondary pulmonary abscess.

The perforation into the pleural cavity (occurring in 2–4% of cases) is a severe complication and its clinical course might be dramatic, even with the development of anaphylactic shock [1]. Hydropneumothorax or pyopneumothorax develops with charcateristic symptoms, physical findings and radiographic images. If the perforated cyst is fertile, a secondary pleural echinococcosis usually develops. In pericardial perforation, cardiac tamponade develops and a fatal outcome is possible.

Vascular or intracardial perforation (very rare, but a highly fatal situation) causes the development of the so called metastatic echinococcosis in different parts of the body [16].

Diagnosis

Laboratory parameters

Patients do not show typical changes. Eosinophilia, which in the past was estimated to be an important sign, is rare (usually occurring after cyst perforation) and is not specific [22]. In inflammatory complications, leukocytosis with a left shift and increased erythrocyte sedimentation rate are observed [21].

Imaging techniques

Radiographic examination is the technique of choice in diagnosis of the disease [13]. The noncomplicated cyst is visualised as rounded and of homogenous opacity of moderate density and with sharp contours. A cyst may cause distal bronchial obstruction, manifested as atelectasis and pneumonitis beyond the cyst. In those cases, differential diagnosis with malignant neoplasms is difficult. Centrally located cysts may compress the bronchovascular structures, presenting radiographically as a depression or indentation at the site of pressure, the so-called notch sign [1].

The appearance of radiographic image of the complications depends on their type [1]. The suppurated cyst is demonstrated by more dense radiographic opacity, nonhomogeneity and with no sharp contours. The ''crescent'' sign has been attributed to the air that enters the perivesicular space, becoming trapped between the adventitia and the unruptured vesicle after vigorous coughing, straining or direct trauma to the cyst, and is the first radiographic sign of impending rupture of the cyst (fig. 1). A double-dome arch sign may appear when a small additional amount of air enters the hydatid vesicle. In total cyst expectoration, a thin, layered ring-like shadow is formed. The ''water lily'' or ''camalote'' sign (a hydro-aerial shadow with undulating upper border) is observed in partially expectorated cysts with folded floating membranes of the cyst. The sign of dry incarcerated membrane (a ring shadow with more dense basal opacity) is typical for total expectoration of the fluid content. The four diagnostic signs described, however, are radiographic rarities. The radiographic pleural manifestations in the acute stage of rupture of a cyst vary from loculated hydropneumothorax to nonloculated partial, complete or tension hydropneumothorax. The water lily sign can also be observed in instances of rupture of the cyst into the pleura. A nodular extrapulmonary appearance suggests secondary hydatidosis of the pleura [1].

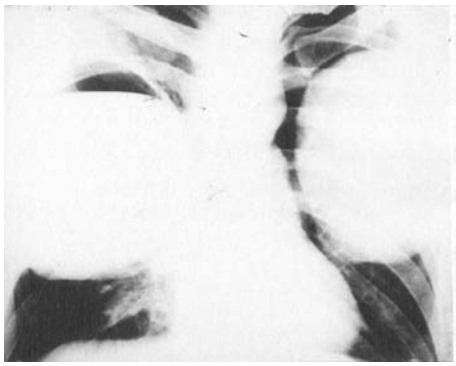


Figure 1. Bilateral pulmonary hydatidosis. The air crescent symptom appears on the right and an uncomplicated enormous cyst on the left.

Computed tomography (CT) has a high sensitivity and specificity for hydatid disease. The CT scan of the thoracic cage is an exceptionally valuable method not only for characterisation of the cyst itself, but also for evaluation of the parenchymatous alterations, the number of cysts and their relationship with the adjacent structures [2]. Intravenous administration of contrast material is not always necessary unless complications are suspected, especially infection and large vessel or heart involvement. Cyst fluid usually demonstrates water attenuation (3–30 Hounsfield units) [17]. The internal septa are easily detected as soft tissue membranes and the detached laminated membrane is frequently visualised as a linear area of increased attenuation within the cyst. Cyst calcification usually occurs in the cyst wall, although internal calcification in the matrix may also be seen. Densely calcified cysts may be assumed to be inactive, but partial calcification of the cyst does not always indicate the death of the parasite. When the cyst wall is heavily calcified, a thick round calcified nodule can be seen. CT is a valuable method for complication detection of rupture into the tracheobronchial tree and suppuration (fig. 2), transdiaphragmatic evolution, chest wall, mediastinal or cardiac involvement [16]. The differential diagnosis includes benign tumours, inflammatory masses, metastases, solid or fluid-filled cysts and carcinomas.

Magnetic resonance imaging (MRI) is not superior to CT scan. The cysts show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images [1]. The signal characteristics differ depending on the developmental phase of the parasite and whether the cyst is viable, infected or dead. When present, daughter cysts are seen as cystic structures attached to the germinal layer that are hypointense relative to the intracystic fluid on T1-weighted images and hyperintense on T2-weighted images. Hydatid cysts may have a low signal-intensity rim on T2-weighted images; this finding has been proposed as a characteristic sign of hydatid disease [17]. It probably represents the outer layer of the hydatid cyst, which is rich in collagen and is generated by the host. Collapsed parasitic membranes appear on MRI as twisted linear structures within the cyst. Although cyst wall calcification is more clearly depicted at CT, MRI is superior in demonstrating irregularities of the rim. These irregularities probably represent incipient detachment of the membranes. Sagittal and coronal magnetic resonance images may well visualise perforated cysts into the vascular system [16, 17], and the migration of the cyst through the diaphragm, allowing accurate pre-surgical diagnosis based on various grades of transdiaphragmatic migration.

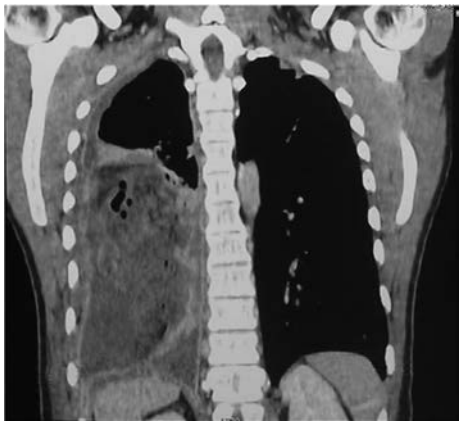


Figure 2. Computed tomography of complicated large right pulmonary hydatid cyst (with perforation into the bronchus and suppuration).

Thoracic ultrasonography is a valuable method in noncomplicated and perforated cysts, especially in children [23] and individuals with a thin thoracic wall.

Abdominal ultrasonography (most frequently) or CT scan are mandatory due to the large rate of combined echinococcosis (the liver is the most frequently affected organ) [24].

Serology tests

Immunodiagnostic tests are used in the diagnosis and follow-up of patients with hydatid cysts. The principal

factor related to a positive serology is the presence or absence of complications (rupture and infection) because of the release of parasite antigens [17].

Due to their low diagnostic value, older serological tests (Casoni, Weinberg, *etc.*) are not used on a routine basis [18]. An ELISA or indirect haemagglutination test is commonly used as an initial screen, and is positive in <50% of patients with pulmonary hydatidosis and >90% of patients with hepatic cysts. Testing for specific antibodies, such as specific immunoglobulin G1 or G4, rather than total immunoglobulin G, may improve the specificity of the test. The specificity of these tests increases considerably when utilising antigen 5 (the arc 5 test), immunoblotting or gel diffusion assay for specific hydatid antigen [17].

Serological testing produces both many false-positive and many false-negative results. False-positive reactions are more likely in the presence of other helminthic infections, cancer and immune disorders. False-negative results occur with varying frequency depending upon the site of the lesion and cyst integrity and viability. A negative serological test does not generally rule out echinococcosis [13].

Invasive techniques

Bronchoscopy is indicated only for the complicated forms and in suspicion of neoplastic process. In ruptured hydatid cyst of the lung, it enables the visualisation of the hydatid membrane, resembling "the shininess of cooked egg white", and small fragments of the cystic membrane can even be removed during bronchoscopic examination [3].

The transthoracic puncture is strictly contraindicated due to the risk of dissemination and anaphylactic shock [1, 23].

Treatment modalities

Despite the existing medical therapy, surgical treatment is the method of choice in the treatment of pulmonary echinococcosis.

Medical treatment

Chemotherapy alone with antihelmintic benzimidazoles (albendazol and mebendazole) is effective and is an alternative for patients with multiple, single intact cysts or relapses [17, 25, 26], and for those who cannot tolerate surgery [27]. However, this strategy is a long and tedious process that carries considerable risk [4].

Albendazole is given in a dose of 10–15 $mg \cdot kg^{-1} \cdot day^{-1}$ for four 30-day courses with or without interval between them [25, 26, 28] and mebendazole is administered in a dose of 30–70 $mg \cdot kg^{-1} \cdot day^{-1}$ for $\geq$6 months [25, 28]. Albendazole is preferred because it has better bioavailability. Both drugs are also contraindicated in pregnancy (especially during the first trimester) because of possible teratogenicity.

The assessment of the chemotherapeutic effectiveness is performed according to the criteria based on the changes of the cyst appearance: success (cure), with evidence of a parasitocidal effect on all cysts; partial success (improvement), with evidence of a parasitocidal effect on some cysts, but with no effect on the other cysts; and failure, with no effect on any cysts [27]. In adults, the cure and partial success rates vary from 25% to 35% and from 68% to 70% of patients, respectively [26], but relapses in ~24% of cases are also observed [28]. In a group of 82 children, 34.1% were cured, 34.1% improved and 31.8% failed [25]. The cure and the failure rates are statistically insignificant in cysts treated with mebendazole and albendazole; however, more cysts are statistically significantly improved with albendazole. There is a positive, weak and statistically significant correlation between the cyst size and treatment results (smaller young cysts are affected more quickly and easily) [25].

The major complications of medical treatment are infection, haemoptysis and anaphylactic shock [25, 29, 30], and the adverse events include hepatotoxicity, neutropenia, gastrointestinal symptoms and alopecia [25, 28]. WEN and YANG [31] found a 77.3% incidence of cyst rupture in 21 patients treated with albendazole. In a group of 36 children treated by chemotherapy, KERAMIDAS *et al.* [29] found 11 complications requiring surgery. They conclude that: 1) large pulmonary hydatid cysts should not be treated medically; 2) incomplete expectoration of the cyst contents after the parasite death may lead to infection through bronchial communication; and 3) patients treated surgically for complications following medical treatment are hospitalised for twice as long as patients treated surgically in the first place.

Surgery

During surgery, a double-lumen endotracheal tube is used, usually to prevent blockage of the tracheobronchial tree by the cyst content during the operation.

Although the muscle-sparing thoracotomy is a less traumatic surgical approach [2, 32], most authors still prefer standard postero-lateral thoracotomy [4, 22, 24, 33, 34].

Video-assisted thoracoscopic surgery (VATS) is introduced in the treatment of the disease, although not very aggressively and predominantly in children, due to its pathomorphological characteristics with the risk of intra-operative dissemination and recurrence [35–39]. If the cyst is complicated, the potential for the infection to spread should also be kept in mind [19]. For these reasons, some authors feel that thoracoscopic techniques should be reserved for dead cysts only [36]. The peripheral cysts of a diameter up to 5 cm are indicated for removal by means of VATS, while the centrally located parasites are not suitable for this approach [5]. The presence of multilocular cysts of a diameter >4 cm, giant cysts, recurrent echinococcosis and suppurated cysts with manifested perifocal inflammation, as well as a history of unilateral thoracotomy on some other occasion, are also contraindications for VATS. Nevertheless, thoracoscopically guided minimally invasive surgery for a giant hydatic cyst is presented in one case [37]. The VATS approach by means of two or three surgical ports follows the same principals to the open technique. A closed circuit of suction (which works in the same way as pleurocan drainage) is prepared, the needle is inserted into the exocyst through the utility incision and the cystic fluid is aspirated [40]. The removal of the hydatid membranes is performed by a standard endobag used in VATS removal of the lung lobes. Conversion to open surgery is not required in most of the series [40, 41], except for one [38]. MEHTA *et al.* [41] present a comparative evaluation of VATS *versus* thoracotomy in the management of lung hydatid disease. In the thoracoscopic group, the post-operative analgesia requirement is less and the intercostal drain is removed earlier than in the thoracotomy group. Although post-operative hospital stay in the VATS group is significantly shorter than in the thoracotomy group (8.35 *versus* 18.77 days), the duration of hospital stay is still longer than of other authors (4–4.5 days) [40]. Thoracoscopy also offers a great advantage over open thoracotomy in terms of very low morbidity [40, 41], although the case of a 10-year-old male who developed a lung abscess after VATS echinococcectomy and had to undergo lobectomy is presented [39]. Presently, VATS removal of superficial and small-to-moderate hydatid cysts is a safe and reliable option [40], and there is a possibility that the indications for VATS in pulmonary echinococcosis could widen with future elaboration of the technique [5].

The principles of surgical treatment should be evacuation of the cyst with removal of the endocyst, avoidance of contamination and management of the residual cavity [24, 42, 43], but the most important point of the operation is to preserve as much tissue as possible. The choice of surgical technique depends on the conditions encountered during the operation. The classic rules of surgical hydatidology are strictly respected. The surgical field is isolated with the help of compresses soaked in 30% saline or povidone–iodine solutions for prevention of intra-operative insemination. Surgical techniques in pulmonary echinococcosis are divided into three major groups: parenchyma-preserving methods, pericystectomy and pulmonary resections (fig. 3).

Organ-sparing extirpation methods

The pathomorphological characteristics of the disease permit only the parasite to be removed and the functionally preserved lung to be spared in a large part of the cases, including complicated cysts with reversible alterations in the neighbouring lung parenchyma. Thus extirpation techniques are assumed to be the method of choice in the surgical treatment of pulmonary echinococcosis in children and adults [14]. A variety of techniques exist both for parasite removal and for treatment of the residual fibrous cavity in lung parenchyma.

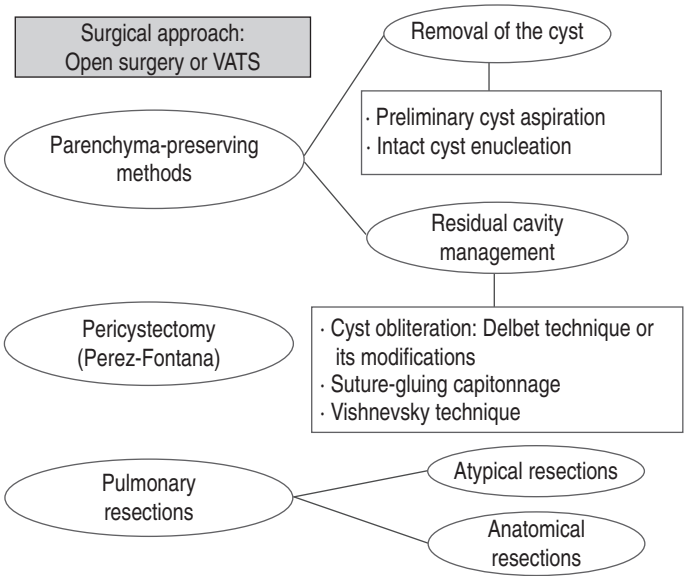


Figure 3. Operative methods for pulmonary hydatidosis. VATS: video-assisted thoracoscopic surgery.

Techniques for hydatid cyst removal

Intact cyst removal

Intact cyst removal is also known as enucleation or the Barrett technique [44]: the Barrett technique is indicated in peripheral noncomplicated cysts of a comparatively smaller size. It has limited application in clinical practice due to the risk of intra-operative dissemination following echinococcus cyst perforation [22] and only few authors use it routinely [42]. The fibrous capsule is cut along two-thirds of the cyst length (fig. 4) and the latter is removed intact through an increase of intrapulmonary pressure [3, 26, 44] or using manual pressure in a collapsed lung [45]. During "delivery" of the cyst, one or two tubes are ready to suction in case of sudden rupture [10].

Removal following preceding cyst puncture

This is the technique preferred by most surgeons in all types of echinococcosis in both children and adults [22, 46]. A large-gauge puncture needle is regularly used [5], but in order to prevent intra-operative insemination, a variety of special trocars or other devices for puncture of the parasite are also recommended [3, 47]. Some authors recommend the use of scoliocidal agents by injecting them into the endocystic cavity to kill protoscoleces [42], but unfortunately this may cause undesirable complications and even death due to leaking of scoliocidal agents into ectocystic cavity where several bronchial openings lie [48].

Figure 4. Intact cyst removal (Barrett technique). The pericystic layer is cut superficially until the laminated membrane of the cyst is seen. This incision is extended to a certain length so that the delivery of the cyst is possible.

Techniques for treating the residual fibrous cavity

Due to the risk of recurrence from viable scolices left behind, the residual capsule is obligatorily treated with various antiscolicidal medicaments [18, 49], freezing

of the cyst wall and instillation of 0.5% silver nitrate solution [50] or ultrasound [51]; most often, a 10% solution of NaCl [9, 23, 44] and 10% povidone–iodine solution are applied [19, 22]. Leaving bronchial fistulae in the fibrous capsule initiates the formation of a residual cavity and suppuration, which makes their eradication mandatory [7, 52]. The presence of bronchial fistulae should be evaluated by filling the residual cavity with sterile solution and inflating the lung. All bronchial leaks that are found should be closed individually. Various techniques and sutures are available; usually absorbable monofilament sutures are preferred [1, 19, 22]. In the VATS approach, the draining bronchi are sutured with the Endoscopic Suturing Device, 10 mm, 34-cm shaft length (COVIDIEN llc, Mansfield, MA, USA) or, very rarely, with monofilament absorbable sutures on an atraumatic needle using a long standard needle holder [5, 26]. A variety of techniques exist for eradication of the residual fibrous cavity after removal of the parasite.

Delbet capitonnage

Delbet capitonnage is a popular technique used in both children and adults [19, 21–24, 26]: originally the cavity is obliterated through suturing with monofilament absorbable purse-string sutures from the bottom up towards its surface (fig. 5). Several modifications exist using various sutures: rectangular, U-like, spiral and continuous sutures of the "aller retour" type [1]. A suture-gluing capitonnage introduces the application of a purse-string suture at 2–3 cm from the residual cavity bottom and gluing the underneath section of the fibrous capsule with glue, the whole cavity is eradicated and the number of necessary sutures for large cysts is decreased [5]. In the VATS approach, the fibrous capsule walls might also be glued with Tissucol fibrin glue (Baxter AG, Vienna, Austria) [52].

ÇELIK *et al.* [53] found that capitonnage could cause atelectasis by obliterating the bronchus surrounding the cyst, thus, they and other authors do not advocate this technique, provided bronchial fistulae are secured [4, 7, 54].

Vishnevsky technique

After removal of large peripheral cysts, the scolicidal processing of the residual cavity and suturing of the draining bronchi, the free ends of the fibrous capsule undergo maximal resection; in this way the bottom of the cavity is converted into a lung surface [4, 15, 55]. According to the original technique the whole diameter of the residual cavity at the border between the parenchyma and the fibrous capsule is sutured with a continuous absorbable suture [55]. Some authors suture only the sections with alveolar leakage and, in large cysts with interlobar location, after removal of the cyst and suturing the draining bronchi in the interlobar space (the residual cavity), additional tube drainage is applied for adequate control of aerostasis and safe closure of the fibrous capsule walls [5]. Thus, the development of encapsulated and completely surrounded by parenchyma residual cavities is avoided.

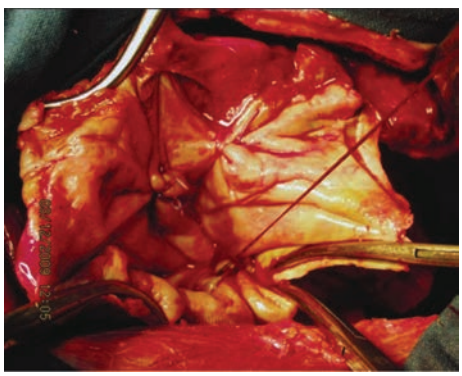


Figure 5. Delbet capitonnage. The cavity is obliterated through suturing with monofilament absorbable purse-string sutures from the bottom towards its surface.

Perez-Fontana technique

This procedure is a pericystectomy and has been recommended for removal of the cyst together with its fibrous capsule [6]. It has been assumed that parasitic elements might be left behind in the capsule, which might cause recurrence. Numerous pathological studies have shown that this procedure is not grounded from a biological point of view. Additionally, a dissection plane between the pericyst and parenchyma does not exist, which creates a risk of haemorrhage. Currently, the technique is seldom used in small peripheral cysts with initial complications [43, 50]. Only BURGOS *et al.* [3] favour it in 86.2% of their case series.

Pulmonary resections

Atypical resections

Atypical resections are most frequently wedge resections and are indicated for small peripheral cysts when rupture or infection is detected [3]. In an open surgical approach, either staplers are used or the resection lines are sutured manually, while in VATS, an Endo-GIA colour code green 60 mm, 4.8-mm (Covidien llc) is applied (fig. 6) [5].

Anatomical resections

Anatomical resections may be justified only when a certain anatomical structure is completely destroyed by a giant cyst or several noncomplicated cysts, as well as in complicated echinococcosis with irreversible alterations in the surrounding lung parenchyma [3, 18, 43]. Reports in the literature note resection rates of 0–7% for uncomplicated pulmonary hydatid cysts, whereas the corresponding figures for complicated pulmonary hydatid cysts are considerably higher at 19–32% [19]. Most frequently, lobectomy or segment resection is applied; pulmonectomy is performed as an exception in multiple or recurring complicated echinococcosis [43]. In cases with intrapleural cyst perforation, ARIBAS *et al.* [9] make use of decortication (69.8%) and pulmonary resection (14%). In empyema cases with trapped lung caused by pleural peel, a decortication is performed to re-expand the lung [18, 23]. Decortication is statistically significantly required in many more patients with complicated cysts compared with noncomplicated echinococcosis [19].

The radical excision (extirpation) is a method of choice in the treatment of intra-thoracic extrapulmonary cysts [14, 15, 17]. An operative procedure of the chest for hydatid cysts includes not only cystectomy, but, due to destruction of the ribs, a requirement for chest wall resection in some cases [14].

A surgical procedure in patients with heart echinococcosis depends on the localisation of the cysts (manipulations take place under cardiopulmonary bypass or off-pump procedure). The removal of a hydatid cyst in the main pulmonary artery is performed with pulmonary arteriotomy *via* sternotomy under total circulatory arrest or cardiopulmonary bypass [16].

Surgical techniques and strategies in bilateral pulmonary echinococcosis

Bilateral pulmonary echinococcosis is observed in 4–26.7% of adult cases, while in children the rate is 10.8–15.5% of those operated on [5, 16, 36]. The necessity for maximal preservation of a functional parenchyma is of special significance in the selection of surgical technique. The anatomical resection is assumed to be a contraindication in a one-stage bilateral surgery. There are limited reports of anatomical resections in such cases, including only one case in the literature of a one-stage bilateral lower lobectomies *via* median sternotomy [5].

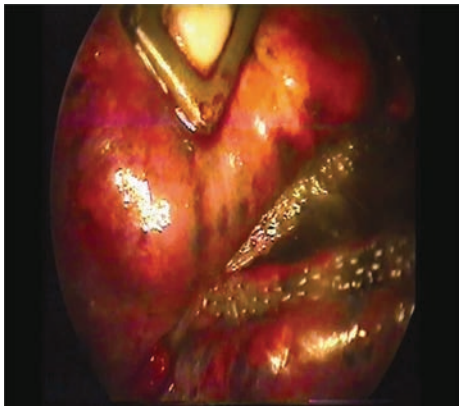


Figure 6. Video-assisted thoracoscopic surgery wedge resection of peripheral complicated hydatid cyst with Endo-GIA 60 mm.

Two-stage technique

Most surgeons prefer a two-stage surgery over different time intervals, usually from 1 to 3 months [14, 34]. First, the complicated cysts or the side with cysts of a higher probability for complications are operated on; thus, the course of the post-operative period is reassured [53]. For the interval between the first and second operation, each patient is informed about possible complications and warned that a second surgery may be needed sooner than planned if the cyst ruptured [19].

Currently, two-stage surgery is mandatory for: 1) multiple bilateral pulmonary cysts; 2) expected lobectomy

accompanied by huge pleural adhesions; 3) significantly reduced cardiopulmonary reserve capacity; and 4) noncompensated chronic conditions or diseases [5].

One-stage technique

The one-stage technique has the following advantages: 1) the patient is operated on only once, thus sparing the repeated psychological and physical trauma; 2) the development of complications in the contralateral cyst during the period between the two surgeries is avoided; 3) the terms of hospital treatment, temporary disablement and social rehabilitation are shortened; and 4) the overall cost for hospital treatment is reduced [5].

According to the surgical approach, the operated patients are divided into the following groups: one-stage consecutive or simultaneous thoracotomies, median sternotomy, transverse trans-sternal approach and bilateral one-stage VATS.

One-stage consecutive or simultaneous thoracotomies

Muscle sparing thoracotomies are preferred. The side with the more severe alterations is the one to start with; after a smooth completion of surgery on the first side, surgery is continued on the other pleural cavity [56]. Very rarely, in the past, simultaneous bilateral surgery performed was practiced by two teams. Submammary bilateral thoracotomies are performed with excellent cosmetic effect, especially in females [5]. However, they are not appropriate for dorsally located cysts and huge pleural adhesions.

Median sternotomy

Median sternotomy is preferred for its comparatively easy performance, adequate exploration and lesser post-operative impairment of respiratory function [5, 11, 53]. Some authors apply it for bilateral cysts with anterior location only [11]. Based on the richest personal experience published in the literature (81 cases), PETROV *et al.* [5] assume that the size, the number and the location of the cysts do not influence the indications for application of this approach. The same is true for the age of the patient, given that his or her cardiopulmonary reserve capacity is preserved and no essential disorders exist in the other organs and systems. It should be emphasised that, in surgery on dorsally located cysts, especially in the left lower lobe, a sudden haemodynamic impairment might occur [5]. A disadvantage of the approach is the unacceptable cosmetic result; this is the reason why recently median sternotomy is not applied, especially in females. Some authors do not recommend median sternotomy because of the risk of infection [18, 23].

Median sternotomy is absolutely contraindicated in the following cases: 1) pleural complications (empyema or intrathoracic evolution of complicated hepatic echinococcosis); 2) severe or irreversible inflammatory alterations in the neighbouring to the cyst parenchyma or the existence of large or extra-large cysts, in which case large anatomical resection is indicated (especially left lower lobectomy); and 3) an impaired general condition of the patient, which is a contraindication for extended surgery. In these cases, the application of two-stage surgery *via* thoracotomy is recommended [5].

Transverse trans-sternal approach ("clamshell incision")

Transverse sternotomy is applied incidentally due to its traumatic nature and the transection of both mammary arteries. A single article finds it as suitable in dorsally located cysts and in association with cardiac echinococcosis [3].

Bilateral one-stage VATS

Only one article exists on the use of consecutive VATS during a one-stage treatment of five patients with bilateral pulmonary echinococcosis [5]. This approach is indicated only in cases with comparatively small bilateral solitary cysts, either intact or complicated with reversible alterations in the neighbouring pulmonary parenchyma. The normal thickness of the patient chest wall is also of essential importance for the selection of this minimally invasive bilateral approach.

Surgical techniques and tactics in associated pulmonary and abdominal echinococcosis

The surgical techniques and tactics used in associated pulmonary and abdominal echinococcosis are determined by the cyst evolution in both body cavities, by the location of the abdominal cysts (liver, spleen, *etc.*), as well as by the general condition of the patient and the existence of severe concomitant diseases [32, 57].

In the case of noncomplicated echinococcosis and selection of a two-stage technique, treatment is usually begun with pulmonary surgery, as, in performing laparotomy as a first stage (especially in large pulmonary cysts), a great probability exists for perforation of the latter due to the elevation of intrapulmonary pressure during anaesthesia [5, 9]. In severe complications of abdominal cysts, the operative treatment should started with laparotomy [5].

Resection is preferred by a large number of surgeons in the treatment of hepatic echinococcosis. It might also be applied in associated pulmonary and hepatic echinococcosis; however, almost all authors apply organ-sparing methods in the treatment of the liver cysts in these cases after securing existing biliar fistulae [9, 24]. Resection is assumed to be obligatory in one-stage surgery, especially in combination with bilateral pulmonary echinococcosis. In such cases, the residual cavity and the remaining pericystic liver tissue are inverted with sutures [24] or echinococcectomy with omentoplasty is recommended without an increase in the percentage of recurrence [2]. The introduction of laparoscopic and VATS surgery [36, 58] and of puncture–aspiration–injection–re-aspiration (PAIR) treatment under ultrasound control in hepatic echinococcosis creates new opportunities for surgical approach in strictly selected patients with associated pulmonary echinococcosis and hepatic echinococcosis, followed by obligatory medical therapy.

In right pulmonary echinococcosis associated with echinococcus at the dome of the liver, a one-stage surgery is recommended *via* thoracotomy and transpleural phrenotomy [12, 13, 24]. In rare occasions, this is also possible in left-sided pulmonary echinococcosis and subphrenical echinococcus location in the left liver lobe [5]. There are authors who drain the residual cavity subdiaphragmatically by means of tube drainage [13], or they suture the edges of the phrenotomy to the fibrous capsule of the residual cavity, thus draining the latter into the pleural cavity [10]. Others make use of primary closure of the hepatic residual cavity [5, 24], followed by the insertion of a drain below the diaphragm in the subphrenic area [24] or without consecutive drainage of the subphrenium [5]. This latter tactics very seldom cause complications and significantly shorten the hospital stay [5].

Still more diverse options for selection of management exist in associated bilateral pulmonary and abdominal echinococcosis, making use of thoracotomies or sternotomy for lung operation [5]. Two-stage operation, sternotomy followed by laparotomy in a general surgery department or PAIR is recommended by KARAOGLANOGLU *et al.* [57]. CERAN *et al.* [8] present the efficacy and cost-effectiveness of one-stage operations in these patients. Sternotomy and right phrenotomy is advocated in dome localisation of hepatic cysts [8, 32, 42]; in such cases, other authors recommend a two-stage operation because of the risk of hepatobiliary fistula [11, 24, 59]. Sterno-laparatomy is carried out in patients with anterior localisation of hepatic cysts [42]. For the first time worldwide, in four patients described by by PETROV *et al.* [5], organ sparing surgery for the three locations (bilateral pulmonary, hepatic and lienal echinococcosis) has been performed together in one stage (fig. 7). The selection criteria for accepting this approach are: 1) a limited number of pulmonary and hepatic cysts (no more than four in each location), which are indicated for removal with organ sparing techniques (this is especially inappropriate for chemotherapy patients); and 2) a small number of peripheral cysts in the spleen, which might be removed *via* echinococcectomy only and without splenectomy. The preconditions for its successful application include: 1) a surgical team experienced in both thoracic and abdominal surgery; 2) the smooth course of the thoracic part of the operation, including a duration that is not prolonged; and 3) adequate post-operative intensive care and respiratory rehabilitation.

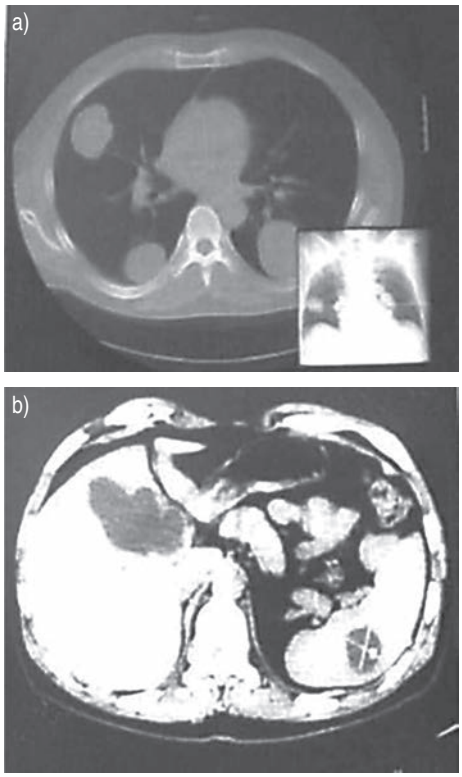


Figure 7. Computed tomography of bilateral pulmonary hydatidosis associated with liver and spleen echinococcosis (one-stage operation by sternolaparotomy). a) Computed tomography of the chest showing bilateral pulmonary cysts. b) Computed tomography of the abdomen showing complicated hepatic cyst and cyst in the spleen.

Pre- and post-operative chemoprevention

Pulmonary hydatid cyst may recur in the same or a different location in the lung [49]. The rate of recurrence in pulmonary echinococcosis varies from 1 to 6%; hence, patients should be reported to a registry and followed up by imaging methods and serology [7, 33]. Reducing recurrence involves a complex treatment of pulmonary echinococcosis (surgical treatment combined with pre- and/or post-operative medicamentous treatment with benzimidazoles). Different authors adhere to various indications using diverse schemes of treatment and medications, as follows: 1) mebendazole (20–40 $mg \cdot kg^{-1}$ daily) for 1 week pre-operatively, with chemotherapy continuing from 6 to 8 weeks post-operatively [42]; 2) mebendazole (50 $mg \cdot kg^{-1}$ daily) or albendazole (10 $mg \cdot kg^{-1}$ daily) for at least 2–3 months in all operated patients [9, 48]; 3) mebendazole (400–600 mg every 8 h) for 7–10 days pre-operatively and, if there is no intra-operative dissemination, this treatment continues up to 1 month post-operatively [60]. In rupture of a cyst or cysts in the pleural cavity, either the treatment is continued for 3–6 months [3], or this treatment is used as three sequential, 28-day courses, with 14-day intervals between courses [24]. Routine albendazole treatment (10 $mg \cdot kg^{-1}$ daily) during the first 15 days of the month for 3 months should be administered in operated patients with bilateral pulmonary echinococcosis [5]. According to the World Health Organization, post-operative chemoprevention is carried out only in the case of intra-operative dissemination and suspicion of residual cysts [27].

Post-operative results

The rate of post-operative morbidity in adults, children and patients with associated pulmonary and hepatic hydatidosis is 3.5–34.8% [3, 4, 18, 19, 33, 34], 12.5.3–25.4% [22, 23, 59] and 3–19% [24, 48, 57], respectively. The most common complications are atelectasis [5, 18, 22, 23, 32, 46], residual pleural cavity [5, 23, 59] and prolonged air leakage [23, 34, 59]. Pneumonia [22, 23], empyema [3], bronchopleural fistula [3, 23, 46], haemorrhage that requires re-exploration [34], chylothorax [19, 61] and wound infection [3, 5, 18] also occur. Post-cystectomy residual cavity [18], which may be infected [46], is a specific complication after "conservative" surgery. Excessive biliary drainage, bronchobiliary fistula and haemorrhage are major complications after surgery for pulmonary and hepatic dome echinococcosis [24, 48].

Post-operative complications are influenced by the size (>10 cm) [22, 33, 57] and number of cysts, and the type of operation (resection techniques) [22, 57]. Other authors claim that surgical technique has no significant effect on post-operative morbidity [23, 54]. Complicated cases have higher rates of pre- and post-operative complications and require longer hospitalisation time and more extensive surgical procedures than uncomplicated cases [19, 23]. This fact underlines the need for immediate surgery in any patient who is diagnosed with pulmonary hydatidosis [19].

There are no fatalities after surgery in recent series of adults [4, 15, 19, 24, 34, 43], children [22, 59] and patients with associated pulmonary and hepatic echinococcosis [48]. The overall post-operative mortality seems to be more frequent in complicated cases [7, 18, 23] and varies from 0.3% to 4.7% [3, 23, 32, 33]. The mortality rate of children operated on late is 11.7%, and 2.1% in early operations [23]; in the large series with bilateral echinococcosis, it is 0.78% (total number of cases=127) [5] and 5% (total number of cases=60) [11], respectively. The overall mortality rate after surgical management of lung and liver dome echinococcosis is also low (0–4.2%) [10]. Post-operative mortality is usually due to pneumonia and sepsis [18, 23], thromboembolism [3, 33] and haemoptysis [3, 23], but some specific causes, such as aspiration of hydatid materials [23] or tension pneumothorax due to dehiscence of the bronchial suture, followed by irreversible cardiac arrest [3], have also been presented.

Conclusions

In conclusion, surgery is the primary mode of treatment for patients with pulmonary echinococcosis. The diversity of the pathological process offers various treatment tactics and approaches (especially in bilateral and associated forms), which must be individually tailored in each and every case. Organ-preserving techniques, by open surgery or VATS, are method of choice. Anatomical resections are justified only when a certain anatomical structure is completely destroyed by a giant cyst or several uncomplicated cysts, as well as in complicated echinococcosis with irreversible changes in the adjacent lung parenchyma. Post-operative chemoprevention is indicated only in cases of intra-operative dissemination and suspicion of residual cysts. Chemotherapy alone is an alternative for patients with multiple, single intact cysts or relapses, and for those who cannot tolerate surgery.

Statement of Interest

None declared.

References

1. Aletras H, Symbas PN. Hydatid disease of the lung. *In:* Shields TW, LoCicero J, Ponn RB, eds. General thoracic surgery. Philadelphia, Lippincott Williams & Wilkins, 2000; pp. 1113–1122.
2. Varela A, Burgos P, Castedo E. Parasitic diseases of the lung and pleura. *In:* Pearson FG, ed. Thoracic and esophageal surgery. New York, Churchill Livingston, 2008; pp. 550–566.
3. Burgos R, Varela A, Castedo E, *et al.* Pulmonary hydatidosis: surgical treatment and follow-up of 240 cases. *Eur J Cardiothorac Surg* 1999; 16: 628–635.
4. Caushi F, Qirjako G, Ciko A, *et al.* Capitonage or not? Which is the best operative technique for hydatid cysts of the lung; when should it be performed? *Pneumonology* 2011; 24: 177–181.
5. Petrov D, Terzinacheva P, Djambazov V, *et al.* Surgical treatment of bilateral hydatid disease of the lung *via* median sternotomy. *Eur J Cardiothorac Surg* 2001; 19: 918–923.
6. Fontana VP. Nouvelle methode operatoire des kystes hydatiques du poumon. [New operative method for pulmonary hydatid cysts.]. *Presse Med* 1949; 41: 593–594.
7. Pejhan S, Zadeh MRL, Javaherzadeh M, *et al.* Surgical treatment of perforated pulmonary cyst. *Tanaffos* 2007; 6: 19–22.
8. Ceran S, Sunam GS, Gormus N, *et al.* Cost-effective and time-saving surgical treatment of pulmonary hydatid cysts with multiple localization. *Surg Today* 2002; 32: 573–576.
9. Aribas OK, Kanat F, Turk E, *et al.* Comparison between pulmonary and hepatopulmonary hydatidosis. *Eur J Cardiothorac Surg* 2002; 21: 489–496.
10. Athanassiadi K, Kalavrouziotis G, Loutsidis A, *et al.* Surgical treatment of echinococcosis by a transthoracic approach: a review of 85 cases. *Eur J Cardiothorac Surg* 1998; 14: 134–140.
11. Cetin G, Dogan R, Yuksel M, *et al.* Surgical treatment of bilateral hydatid disease of the lung *via* median sternotomy: experience in 60 consecutive patients. *J Thorac Cardiovasc Surg* 1988; 36: 114–117.
12. Yoruk Y, Yalcmkaya S, Coskun I, *et al.* Simultaneous operation for coexisting lung and liver hydatid cysts: a treatment modality. *Hepatogastroenterology* 1998; 45: 1831–1832.
13. Peleg H, Best LA, Gaitini D. Simultaneous operation for hydatid cysts of right lung and liver. *J Thorac Cardiovasc Surg* 1985; 90: 783–787.

14. Isitmangil T, Sebit S, Tunc H, *et al.* Clinical experience of surgical therapy in 207 patients with thoracic hydatidosis over a 12-year-period. *Swiss Med Wkly* 2002; 132: 548–552.
15. Yaldiz S, Gursoy S, Ucvet A, *et al.* Capitonnage results in low postoperative morbidity in the surgical treatment of pulmonary echinococcosis. *Ann Thorac Surg* 2012; 93: 962–966.
16. Halezeroglu S, Okur E, Tanyü MO. Surgical management for hydatid disease. *Thorac Surg Clin* 2012; 22: 375–385.
17. Morar R, Feldman C. Pulmonary echinococcosis. *Eur Respir J* 2003; 21: 1069–1077.
18. Cobanoglu U, Sayır F, Sehitoğlu A, *et al.* Therapeutic strategies for complications secondary to hydatid cyst rupture. *Int J Clin Exp Med.* 2011; 4: 220–226.
19. Kuzucu A, Soysal Ö, Özgel M, *et al.* Complicated hydatid cysts of the lung: clinical and therapeutic issues. *Ann Thorac Surg* 2004; 77: 1200–1204.
20. Özpolat B, Sayın M, Dogan OV, *et al.* Simultaneous traumatic rupture of bilateral pulmonary hydatid cysts. *Thorac Cardiovasc Surg* 2005; 130: 908–909.
21. Ozyurtkan MO, Balci AE. Surgical treatment of intrathoracic hydatid disease: a 5-year experience in an endemic region. *Surg Today* 2010; 40: 31–37.
22. Kosar A, Orki A, Haciibrahimoglu G, *et al.* Effect of capitonnage and cystotomy on outcome of childhood pulmonary hydatid cysts. *J Thorac Cardiovasc Surg* 2006; 132: 560–564.
23. Balci AE, Eren N, Eren S, *et al.* Ruptured hydatid cysts of the lung in children: clinical review and results of surgery. *Ann Thorac Surg* 2002; 74: 889–892.
24. Kurul IC, Topcu S, Altinok T, *et al.* One-stage operation for hydatid disease of lung and liver: principles of treatment. *J Thorac Cardiovasc Surg* 2002; 124: 1212–1215.
25. Doğru D, Kiper N, Özçelik U, *et al.* Medical treatment of pulmonary hydatid disease: for which child? *Parasitol Int* 2005; 54: 135–138.
26. Horton R. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. *Acta Tropica* 1997; 32: 171.
27. WHO Informal Working Group on Echinococcosis in Humans. Guidelines for treatment of cystic and alveolar echinococcosis. *Bull World Health Organ* 1996; 73: 231–242.
28. Stojkovic M, Zwahlen M, Teggi A, *et al.* Treatment response of cystic echinococcosis to benzimidazoles Stojkovic: a systematic Review. *PLoS Negl Trop Dis* 2009; 3: e524.
29. Keramidas D, Mavridis G, Soutis M, *et al.* Medical treatment of pulmonary hydatidosis: complications and surgical management. *Pediatr Surg Int* 2004; 19: 774.
30. Kurkcuoglu IC, Eroglu A, Karaoglanoglu N, *et al.* Complications of albendazole treatment in hydatid disease of the lung. *Eur J Cardiothorac Surg* 2002; 22: 649–650.
31. Wen H, Yang WG. Public health importance of cystic echinococcosis in China. *Acta Tropica* 1997; 67: 133–145.
32. Ulkü R, Yilmaz HG, Onat S, *et al.* Surgical treatment of pulmonary hydatid cysts: report of 139 cases. *Int Surg* 2006; 91: 77–81.
33. Ayed AK, Alshawaf E. Surgical treatment and follow-up of pulmonary hydatid cyst. *Med Princ Pract* 2003; 12: 112–116.
34. Safioleas M, Misiakos EP, Dosios T, *et al.* Surgical treatment for lung hydatid disease. *World J Surg* 1999; 23: 1181–1185.
35. Becmeur F, Chaouachi B, Dhaoui R, *et al.* Video-assisted thoracic surgery of hydatid cysts of the lung in children. *J Chir (Paris)* 1994; 131: 541–543.
36. Chowbey PK, Shah S, Khullav R. Minimal access surgery for hydatid disease: laparoscopy, thoracoscopic and retroperitoneal approach. *J Laparoendosc Avd Surg Tech A* 2003; 13: 159–165.
37. Oto O, Silistreli E, Erturk M, *et al.* Thoracoscopic guided minimally invasive surgery for giant hydatic cyst. *Eur J Cardiothor Surg* 1999; 16: 494–495.
38. Parelkar SV, Gupta RK, Shah H, *et al.* Experience with video-assisted thoracoscopic removal of pulmonary hydatid cysts in children. *J Pediatr Surg* 2009; 44: 836–841.
39. Tullu MS, Lahiri KR, Kumar S, *et al.* Minimal access therapy in pediatric pulmonary hydatid cyts. *Pediatr Pulmonol* 2005; 40: 92–95.
40. Alpay LT, Lacin TC, Atinkaya C, *et al.* Video-assisted thoracoscopic removal of pulmonary hydatid cysts. *Eur J Cardiothorac Surg* 2012; 42: 971–975.
41. Mehta KD, Gundappa R, Contractor R, *et al.* Comparative evaluation of thoracoscopy *versus* thoracotomy in the management of lung hydatid disease. *World J Surg* 2010; 34: 1828–1831.
42. Dhaliwal RS, Kalkat MS. One-stage procedure for bilateral lung and liver hydatid cyst. *Ann Thorac Surg* 1997; 64: 338–341.
43. Dogan R, Yuksel M, Cetin G, *et al.* Surgical treatment of hydatid cysts of the lung: report on 1055 patients. *Thorax* 1989; 44: 192–199.
44. Barrett NR, Thomas D. Pulmonary hydatid disease. *Br J Surg* 1954; 40: 222.
45. Benzo M. Nesedidad de la enucleation integra de la hidatide en los quistes hidaticos pulmonares. [The need for intact enucleation of the hydatid in pulmonary hydatid cysts.]. *Rev Hosp General* 1968; 8: 30–36.
46. Tor M, Atasalihi A, Altuntas N, *et al.* Review of cases with cystic hydatid lung disease in a tertiary referral hospital located in an endemic region: a 10 years' experience. *Respiration* 2000; 67: 539–542.

47. Santini M, Fiorello A, Vicidomin G, *et al.* A home-made device for safe intraoperative aspiration of pulmonary hydatid cysts. *Interact Cardiovasc Thorac Surg* 2008; 7: 365–367.
48. Sahin E, Enon S, Cangir AK, *et al.* Single-stage transthoracic approach for right lung and liver hydatid disease. *J Thorac Cardiovasc Surg* 2003; 126: 769–773.
49. Arinc S, Alpay L, Okur E, *et al.* Recurrent pulmonary hydatid disease: analysis of ten cases. *Surg Today* 2008; 38: 983–986.
50. Saidi F, Nazarian I. Surgical treatment of hydatid cysts by freezing of cyst wall and instillation of 0.5 per cent silver nitrate solution. *N Eng J Med* 1971; 284: 3–7.
51. Biriukov YV, Streliaeva AV, Sadikov, *et al.* Obrabotka polosti kisti pri hidatidnom ehinokokoze (eksperimentalnoe-klinicheskoe izsledovanie). [Treatment of residual fibrous cavity in cystic echinococcosis (experimental and clinical study).] *Hirurgia* 2000; 27–29.
52. Uchikov AP, Shipkov Ch, Prisadov G. Treatment of lung hydatidosis by VATS: a preliminary report. *Can J Surg* 2004; 47: 381.
53. Çelik M, Senol C, Keles M, *et al.* Surgical treatment of pulmonary hydatid disease in children: report of 122 cases. *J Pediatr Surg* 2000; 35: 1710–1713.
54. Turna A, Yilmaz MA, Haciibrahimoglu G, *et al.* Surgical treatment of pulmonary hydatid cysts: is capitonnage necessary? *Ann Thorac Surg* 2002; 74: 191–195.
55. Vishnevsky AA. Khirurgicheskomu lecheniu ehinokoka legkih. [About surgical treatment of pulmonary echinococcosis.]. *Vest Hir* 1956; 11: 74–77.
56. Galindo R, Cherkaoui O, Abdelaoui A, *et al.* Le traitement du kyste hydatique pulmonaire ches l'enfant. [Treatment of pulmonary hydatid cysts in children.]. *Ann Chir* 1981; 35: 213–215.
57. Karaoglanoglu N, Eroglu A, Polat KY. Surgical procedure for bilateral lung and liver hydatid cysts. *Ann Thorac Surg* 1998; 66: 988–989.
58. Alper A, Emre A, Hazar H, *et al.* Laparoscopic surgery of hepatic hydatid disease: initial results and early follow-up of 16 patients. *World J Surg* 1995; 19: 725–772.
59. Topcu S, Kurul IC, Tastepe I, *et al.* Surgical treatment of pulmonary hydatid cysts in children. *J Thorac Cardiovasc Surg* 2000; 120: 1097–1101.
60. Bekhti A, Schaap JP, Capron M, *et al.* Treatment of hepatic hydatd disease with mebendazole: preliminary results in four cases. *BMJ* 1977; 2: 1047–1051.
61. Smati B, Sadok Boudaya M, Marghli A, *et al.* Prise en charge des chylothorax post operatoires. [Management of postoperative chylothorax.]. *Rev Mal Respir* 2006; 23: 152–156.

Chapter 11

Mediastinitis: causes, management and outcomes

Stefano Elia[*], *Adelheid End*[#], *Emilio Canalis*[¶], *Hartmut Lode*[+], *Alessandra Vittoria Granai*[§] *and Giuseppe Petrella*[§]

SUMMARY: The term mediastinitis refers to inflammation of the tissues located in the mediastinal space. Many aetiological factors contribute to acute and chronic infection of the mediastinum. Although long recognised as a complication of certain infectious diseases, most cases of acute mediastinitis follow oesophageal perforation and open chest surgery. Less common causes include tracheal, bronchial perforation or direct infection from adjacent tissues. Acute mediastinitis is a life-threatening condition that is almost always a complication of other clinical problems. Chronic fibrosing mediastinitis is a slow deposition of thick fibrous tissue encasing any of the mediastinal structures, most commonly secondary to tuberculosis, histoplasmosis, other fungal infections, cancer or sarcoidosis. Descending necrotising mediastinitis is the most dreaded and lethal form of mediastinitis originating from oropharyngeal infection that extends through the deep neck planes to the mediastinum. The clinical spectrum ranges from the subacute to the fulminate critically ill patient, and therefore early diagnosis and prompt aggressive medical and surgical treatment are required to prevent death.

[*]General Thoracic Surgery, Tor Vergata University, and [§]General Surgery, Policlinico Tor Vergata University, Rome, Italy. [#]Dept of Thoracic Surgery, Medical University of Vienna, Vienna, Austria. [¶]Thoracic Surgery Service, Hospital Universitari Joan XXIII, URV, IISPV, Tarragona, Spain. [+]Dept of Chest and Infectious Diseases, Chest Hospital Heckeshom, Berlin, Germany.

Correspondence: S. Elia, General Thoracic Surgery, Policlinico Tor Vergata University, Viale Oxford, 81, I-00133 Rome, Italy.
Email: elia@med.uniroma2.it

Eur Respir Monogr 2013; 61: 122–140.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041412
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Mediastinitis is an inflammation of connective tissue that involves mediastinal structures and fills interpleural spaces [1]. It derives from infectious or noninfectious causes and, depending on the aetiology, it can be acute or chronic. In its acute form, it is a life-threatening condition with an extremely high mortality rate if recognised late or treated inadequately. Most cases are associated with cardiovascular operations and, although the proportion is rather small, the overall number of patients is considerable [2, 3]. Other aetiologies include oesophageal perforation, tracheobronchial perforation, mediastinal extension of pulmonary infections or mediastinal extension of head and neck infections. When the condition has an infectious origin from the cervical or oral region, such as retropharyngeal abscess, Ludwig's angina [4], thyroiditis or odontogenic infection, the mediastinal inflammation is called descending necrotising mediastinitis (DNM). In this case, the acute polymicrobial infection with extensive fascial necrosis spreads toward the underlying muscles along the neck layers

down to the mediastinum [5]. DNM must be considered a real emergency due to its high mortality rate if left untreated.

Anatomical key points

The mediastinum extends from the thoracic inlet superiorly to the diaphragm inferiorly, and is limited anteriorly from the sternum and posteriorly from the spine, lying between the right and left pleural cavities in and near the median sagittal plane of the chest. It contains many vital structures, such as heart and great vessels, the trachea and bronchi, the nervous system and the oesophagus, but not the lungs. All of the mediastinal structures are surrounded by loose connective tissue and fat. For purposes of description, the mediastinum can be divided into an upper portion, above the pericardium, which is named the superior mediastinum, and a lower portion, below the upper level of the pericardium [6]. The lower portion may be further subdivided into three parts, that in front of the pericardium, the anterior mediastinum; that containing the pericardium and its contents, the middle mediastinum; and that behind the pericardium, the posterior mediastinum.

The superior mediastinum is that portion of the interpleural space that lies between the manubrium sterni in front, and the upper thoracic spine behind. It is bounded below by a slightly oblique plane passing backwards from the junction of the manubrium and body of the sternum to the lower part of the body of the fourth thoracic vertebra, and laterally by the pleurae. It contains the origins of the sternohyoid and sternothyroid muscles and the lower ends of the longus colli muscle; the aortic arch; the innominate artery and the thoracic portions of the left common carotid and the left subclavian arteries; the innominate veins and the upper half of the superior vena cava; the left highest intercostal vein; the vagus, cardiac, phrenic and left recurrent nerves; the trachea, oesophagus and thoracic duct; the remains of the thymus; and some lymph nodes.

The anterior mediastinum predominates on the left side where the left pleura diverges from the mid-sternal line. It is limited in front by the sternum, laterally by the pleurae, and behind by the pericardium. It is narrow above but widens out a little below. Its anterior wall is formed by the left transversus thoracis and the fifth, sixth and seventh left costal cartilages. It contains a quantity of loose areolar tissue, some lymphatic vessels that ascend from the convex surface of the liver, two or three anterior mediastinal lymph nodes, and the small mediastinal branches of the internal mammary artery.

The middle mediastinum, the broadest part of the interpleural space, contains the heart enclosed in the pericardium, the ascending aorta, the lower half of the superior vena cava with the azygos vein opening into it, the bifurcation of the trachea and the two bronchi, the pulmonary artery dividing into its two branches, the right and left pulmonary veins, the phrenic nerves and some bronchial lymph glands.

The posterior mediastinum is an irregular triangular space parallel to the spine; it is bounded in front by the pericardium above, and by the posterior surface of the diaphragm below, behind by the spine from the lower border of the fourth to the twelfth thoracic vertebra, and on either side by the mediastinal pleura. It contains the thoracic part of the descending aorta, the azygos and the two hemiazygos veins, the vagus and splanchnic nerves, the oesophagus, the thoracic duct and some lymph nodes.

Throughout the fetal period, the neck, chest and abdomen communicate with each other and the mediastinum is the anatomical duct. The communications between these anatomical spaces usually seal as the cervico-thoracic organs form and as the body stretches cephalocaudally. Nonetheless, even in adults, remnants of these passageways may allow oro-cervical infection to reach the thoracic cavity and extend to the mediastinum.

Acute mediastinitis

Acute mediastinitis is a serious clinical condition characterised by infection involving the connective tissue that fills the interpleural spaces and surrounds the median thoracic organs; it is almost always a complication of other clinical problems. Although relatively uncommon, it is associated with high mortality if left untreated. The infection of the sterile mediastinal space leads to a systemic inflammatory response syndrome. Severe sepsis or septic shock develops if it is impossible to surgically control the infection and limit the inflammatory process. Unsatisfactory treatment will lead to multiorgan dysfunction syndrome or multiorgan failure, as well as other complications and death. Oesophageal perforation and median sternotomy are the most common causes, followed by tracheal perforation, foreign body retention, malignancy invading the mediastinum, suppuration of mediastinal lymph nodes, descending infection from the neck, or extension of infection from the lung, pleural space, vertebrae and sternum (table 1). The pathological features of acute mediastinitis are those of a severe inflammation in the mediastinal soft tissues that may bring in its late evolution to abscess development. The microbiology is related to cardiothoracic surgery and suction of oesophageal content, while that secondary to odontogenic or other head and neck infections is remarkably different [7, 8], as summarised in table 2.

Clinical findings

Symptoms of acute mediastinitis generally have a sudden onset and include chills, high fever, tachycardia, sepsis, lethargy, respiratory distress, dysphagia and evidence of extreme toxicity. Tachypnoea and pain on swallowing might also be present. The involvement of upper mediastinum is characterised by retrosternal pain radiating upward into the neck, and a sensation of earache. When the inferior–posterior zone is mainly affected, the pain is mostly intrascapular and sometimes surrounds the chest. An early-stage physical examination is usually not diagnostic, but if an oesophageal perforation is the originating cause there may be cervical tenderness, cervical

Table 1. Aetiological factors in acute mediastinitis

Sternotomy complications after cardiothoracic surgery
Coronary artery bypass grafting, cardiac valve replacement, repair of congenital heart defect, heart transplantation, heart–lung transplantation, cardiac-assist devices
Oesophageal perforation
Iatrogenic
Oesophagogastroduodenoscopy, oesophageal dilatation, oesophageal variceal sclerotherapy, nasogastric tube, Sengstaken–Blakemore tube, endotracheal intubation, oesophageal surgery, para-oesophageal surgery, radiation-associated necrosis
Swallowed foreign bodies
Bone, coins, can pull-tabs, drug-filled condoms, swords, caustic agents
Trauma
Penetrating: gunshot wound, knife wound
Blunt: steering wheel injury, seat belt injury, cardiopulmonary resuscitation, whiplash injury, barotrauma
Spontaneous or other
Emesis (Boerhaave's syndrome, Mallory–Weiss syndrome), cricoid pressure during anaesthesia induction, heavy lifting, defecation, parturition, erosion of the oesophageal wall by malignant tumour, perforation following burn of oesophagus
Tracheobronchial perforation
Penetrating or blunt trauma, rigid or flexible bronchoscopy, endoscopic laser treatment of tracheobronchial malignancies, post-intubation tracheal rupture
Head and neck infections
Odontogenic, Ludwig's angina, pharyngitis, tonsillitis, parotitis, epiglottitis
Chronic fibrosing mediastinitis due to granulomatous infections
Infection originating at another site
Pneumonia, lung abscess, pleural space infection or empyema, subphrenic abscess, pancreatitis, cellulitis or soft tissue infection of the chest wall, osteomyelitis of sternum, clavicle, ribs or vertebrae, haematogenous spread from distant foci

Table 2. Microbiology of mediastinitis

Organisms frequently recovered in mediastinitis secondary to infection of the head and neck or oesophageal perforation
Peptostreptococcus spp., *Actinomyces*, *Eubacterium*, *Lactobacillus*, *Veillonella*, *Bacterioides* spp., *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp., *Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium*, *Branhamella*, *Enterobacteriaceae*, *Pseudomonas* spp., *Eikenella corrodens*, *Candida albicans*
Organisms recovered in mediastinitis secondary to cardiothoracic surgery
Staphylococcus aureus (MRSA), *Staphylococcus epidermidis*, *Enterococcus* spp., *Streptococcus* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *C. albicans*
Others occasionally reported
Acinobacter, *Legionella* spp., *Bacteriodes fragilis*, *Corynebacterium* spp., *Mycoplasma hominis*, *Candida tropicalis*, *Nocardia* spp., *Kluyvera*, *Mycobacterium fortuitum*, *Mycobacterium chelonei*, *Rhodococcus bronchialis*
Other unusual causes of mediastinitis
Anthrax, *Brucellosis*, actinomycosis, paragonimiasis, *Streptococcus pneumoniae* infection

MRSA: methicillin-resistant *Staphylococcus aureus*.

cellulitis and subcutaneous emphysema. All of these symptoms usually appear 24–48 h after the stimulation process. Compression of mediastinal structures may cause 1) a superior vena cava syndrome or unilateral obstruction of brachiocephalic veins; 2) different blood pressure values between the two arms due to compression of brachiocephalic arteries; 3) dyspnoea, stridor and obstructed breathing when the trachea is involved; and 4) chylothorax or chylous ascites from obstruction of the thoracic duct. More rare events include hoarseness from recurrent laryngeal nerve involvement, diaphragmatic paralysis from phrenic nerve pressure, tachycardia from involvement of the vagus nerve, or Horner's syndrome due to injury to a stellate ganglion.

Radiological findings

Chest radiographs do not necessarily show mediastinal widening and, therefore, further investigations are always advisable [9, 10]. Air is usually present after rupture or perforation of the oesophagus, trachea or bronchi, and a computed tomography (CT) scan will show mediastinal widening and air–fluid levels, diffuse or focal ectopic gas bubbles, focal mediastinal soft tissue masses and abscesses, often in association with pleural effusion (fig. 1).

Based on CT imaging, acute mediastinitis can be categorised into three patterns: 1) diffuse mediastinitis; 2) isolated mediastinal abscess; and 3) empyema or subphrenic abscess complicating a mediastinitis or mediastinal abscess [9]. In a retrospective study on 40 patients with suspected acute mediastinitis, including 28 post-operative patients, five with acute DNM, and seven with suspected post-traumatic perforation of the oesophagus, CT findings were attenuation of mediastinal fat (100%), localised mediastinal fluid collections (55%), free gas bubbles in the mediastinum (57.5%), mediastinal lymph nodes (35%), pericardial effusions (27.5%), pleural effusions (85%), lung infiltrates (35%), sternal dehiscence (40%) and pleuromediastinal fistula (2.5%). The sensitivity and specificity of CT in post-operative patients in the first 17 days was 100% and 33%, respectively, and after day 17, 100% and 90%. In patients with acute DNM sensitivity was 100% while in patients with suspected oesophageal perforation sensitivity and specificity were 100% [11].

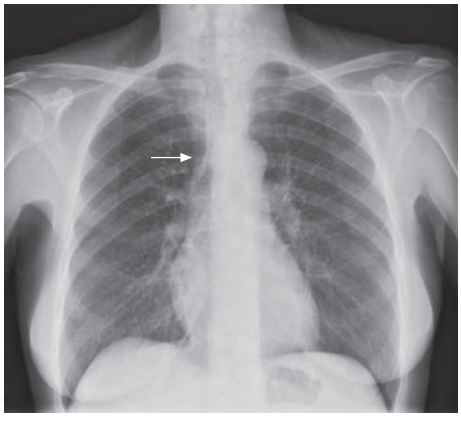


Figure 1. Plain antero-posterior chest radiograph in a patient with suspected descending necrotising mediastinitis at admission. Arrow shows mediastinal widening.

Mediastinitis due to oesophageal perforation

Mediastinitis secondary to oesophageal perforation may follow damage to the oesophagus due to trauma, malignancy or spontaneous causes. Trauma is usually seen after surgery, endoscopy or interventional radiology procedures. An oesophageal perforation may follow difficult or emergency tracheal intubation, especially in elderly patients or in concomitant oesophageal malignancy. In such cases, the lesion is caused by the extremity of the endotracheal probe and occurs predominantly at the weakest region, namely, Laimer's triangle between the cricopharyngeal muscle and the laryngeal constrictor muscle. Patients with poor coordination of swallowing action or malfunctioning of the upper oesophageal sphincter may accidentally swallow sharp pieces of food, such as chicken bones, that occasionally perforate the oesophagus. Primary oesophageal malignancy or infiltration from lung neoplasm may cause rupture secondary to weakening of the oesophageal wall, while post-operative leakage from oesophageal anastomosis can be another aetiological factor. Laceration of the oesophagus may also follow accidental or intentional intake of caustic agents. Spontaneous perforation is typical of Boerhaave's syndrome after forceful vomiting [12].

The onset of infection due to oesophageal perforation is enhanced by the dynamics of breathing, as the fluctuations in negative intrathoracic pressures tend to suck oesophageal contents, including air, saliva, digestive enzymes, bile, acid food and bacteria, into the mediastinum.

The clinical signs and symptoms are negligible, if the perforation is limited to the mediastinum or is between the mediastinum and visceral pleura. The CT pattern of oesophageal perforation is characterised by oesophageal wall thickening, fluid collection in the mediastinal or lower cervical areas, extra-luminal air and output of ingested contrast material into the mediastinum or pleural space. Pneumothorax and hydropneumothorax may be an additional finding. Prompt diagnosis of oesophageal perforation is mandatory to carry out the appropriate treatment that might be either conservative or surgical. Nonoperative treatment is usually applied in cases of intramural perforation or when a transmural perforation is not accompanied by signs of systemic sepsis or underlying malignancy. Usually the medical treatment involves exclusion of oral feeding by establishment of parenteral hyperalimentation and *i.v.* administration of broad spectrum antibiotics, such as tetracyclines and nitroimidazoles. Operative treatment strategies can be subdivided into conservative, reconstructive and radical surgical interventions. Conservative treatment includes drainage, T tube or endoprosthesis insertion and finally oesophageal exclusion or diversion.

Direct closure is feasible within 24 h after perforation, with survival rates approaching 80% [12], and is often performed with reinforcement by a pleural or pericardial flap. Pedicled omental, intercostal muscle and diaphragmatic flaps may also be used. The more delayed the treatment, the worse is the expected prognosis. Recently, endoscopic positioning of coated self-expandable stents and internally applied clips, combined with radiologically guided drainage, has replaced reconstructive surgery in the early stages of disease, but stent removal time is still challenging.

Post-surgical mediastinitis

Post-operative mediastinitis is the second most common acute mediastinitis and usually occurs following sternotomy for performing cardiovascular surgery. The complication rate (0.5–5%) of median sternotomy itself is low, but mediastinitis is associated with high mortality (7–80%) and morbidity [13], particularly in the post-operative setting following coronary artery bypass grafting (CABG) with an incidence rate of 1–2% in large surgical centres [3, 14]. Certain subsets of patients, such as those that have undergone heart or lung transplant, are even at higher risk [15].

Pre-operative, intra-operative and post-operative predisposing factors include lengthy cardiopulmonary bypass time, diabetes, obesity, chronic obstructive pulmonary disease and the need

for prolonged post-operative medical ventilation. The use of pedicled bilateral internal mammary artery (BITA) grafts carries increased risk for mediastinitis after CABG, but this risk is reduced if skeletonised BITA grafts are used [16]. Tracheostomy, mostly if performed early after median sternotomy when contamination occurs by adjacent extension all the way through unsealed tissue planes, and blood transfusion may increase the risk of mediastinitis [17, 18].

The typical patient with post-operative mediastinitis presents with local signs, such as pain, tenderness, erythema and sternal instability or click, accompanied by systemic signs, such as fever, sepsis, increased erythrocyte sedimentation rate and white blood cell count. Up to two-thirds of patients present within 14 days following surgery. The Hamman's sign, namely a crunching sound over the precordium during systole, should alert the physician to possible mediastinitis. Direct signs of sternal infection may be among the initial presenting signs, but distinction between a superficial wound infection and a deeper chest infection associated with mediastinitis may be challenging. The presence of systemic signs of sepsis suggests mediastinal involvement. Diagnosis requires a careful radiological investigation, which can only be accomplished by CT scan, as conventional techniques may not distinguish post-operative haemorrhage and oedema from a mediastinal infection [19]. Usually small anterior mediastinal fluid or air collections may persist for weeks after removal of drains, while a large, low-density fluid collection in the retrosternal area in a febrile patient mandates surgical exploration. The previous sternotomy should be revised and reopened, and all necrotic and infected tissue removed. The sternum is carefully separated from the ventricle bypass grafts and the aorta to avoid bleeding. Samples of necrotic tissue and fluid collection are sent to microbiology for culture and antibiogram in order to prompt adequate targeted antibiotic therapy. *Staphylococcus* species-induced mediastinitis demand *i.v.* administration of a combination of cefamandole, vancomycin and gentamicin. *Staphylococcus aureus* is the most common isolated bacterium in patients developing mediastinitis, and has become an evolving management problem because of an increasing number of antibiotic resistance and methicillin-resistant *S. aureus* (MRSA) infections with high rates of morbidity and mortality. Even though vancomycin is still the antibiotic of choice for the treatment of infections caused by MRSA, it may be contraindicated in a number of cases (*e.g.* renal failure) and be ineffective because of limited tissue penetration; therefore, alternative antibiotics, such as linezolid and daptomycin, are under investigation to solve these problems [20].

Delayed closure may be performed either with pectoralis or rectus abdominis muscle flaps. Omental flaps are used, as well as a two-step procedure after at least three consecutive negative pericardial cultures, by transferring the greater omentum along with the right gastroepiploic artery into the pericardial cavity in order to eliminate the dead space. A recent review of best evidence papers on this topic has outlined the pros and cons of both techniques, suggesting a careful selection of patients, as no obvious advantage of muscle flap over omental flap has been ascertained [21]. Successful delayed vacuum-assisted healing has also been reported in a recent review [22].

Mediastinitis secondary to osteomyelitis

Mediastinitis secondary to osteomyelitis is extremely rare and results from neighbouring spread of adjacent bone and joint infections. The infection of sternoclavicular joint is often associated with secondary mediastinitis due to its close relationship with the anterior mediastinum. Tuberculosis (TB) or fungal osteomyelitis is more common than other infective causes. Most patients have an underlying debilitating systemic disease, such as diabetes mellitus or rheumatoid arthritis or a history of drug-addiction. Possible findings include cortical destruction, increased mediastinal fat attenuation up to obliteration of fat planes around vessels, and mediastinal abscess. The treatment of uncomplicated sternoclavicular infections is based on antibiotics alone, and mediastinal drainage, if necessary, is accomplished by mediastinotomy.

Acute DNM

Aetiology

DNM is one of the most fatal forms of mediastinitis that usually occurs as an unexpected complication of odontogenic or cervicofascial infections or, more rarely, after cervical trauma. The main feature of this type of complex disease is its capacity to involve crossing several anatomical compartments and cause fasciitis and muscle necrosis, cellulitis, abscess formation and overall systemic toxicity with spread along the deep fascial planes of the neck into the mediastinum due to their close relationship. The exact knowledge of neck anatomy and the mechanism of propagation along the fascial planes is crucial for the thorough understanding of DNM and to establish a correct treatment strategy [5, 23–26]. The deep fascia of the neck is divided into three layers [27], which form three major fascial pathways into the deep neck along which oropharyngeal infections can spread to the mediastinum. The three layers are the pre-tracheal, the perivascular and the pre-vertebral spaces.

The pre-tracheal or superficial space is located anterior to the trachea and posterior to the pretracheal fascia and is the most superficial space. The upper limit is given by the thyroid cartilage, while the bottom contour of this space is the pericardium and parietal pleura at the level of carina. Infections in this space cause suppurative pericarditis and empyema [28].

The perivascular, lateropharyngeal or visceral space is wrapped by the carotid sheath that includes the vagus nerve, carotid artery and internal jugular vein. The carotid sheath takes its origin from the fusion of all three major layers of the deep cervical fascia, thus originating a potential pathway for DNM into the chest, draining into middle mediastinum and pleural spaces from the base of the skull to the aortic arch along the so-called ''Lincoln's highway'' [29].

The pre-vertebral or retrovisceral split of the deep layer of the deep cervical fascia runs from the skull base to the coccyx, anterior to the vertebrae and firmly attached to the spine and paraspinous muscles. The alar fascia divides this space into two sections, the anterior or retropharyngeal pathway located between the oesophagus and spine that, if infected, can prompt a posterior mediastinitis [5], and the most posterior, starting at the C6 level of the spine and continuing as far as the T1 level (where the alar fascia joins the inferior constrictor muscles of the pharynx). The latter is the so-called ''danger space'', as it is patent from the skull base to the diaphragm, and lies behind the oesophagus through the superior and posterior mediastinum [23, 26, 28]. When a retropharyngeal abscess ruptures through the alar fascia and infection reaches this level, the prognosis is usually poor [30, 31].

Retropharyngeal pathway accounts for ~70% of the cases of DNM, while another 8% occur *via* the pretracheal route, secondary to suppuration originating from thyroid gland [27, 32]. In all other cases, the perivascular spreading is occasionally complicated by arterial haemorrhage. Most usually, pharyngeal abscesses spread through the retropharyngeal space to the posterior mediastinum, whereas submental and submaxillary abscesses reach the anterior mediastinum [33]. Moreover, the middle layer of the deep cervical fascia fuses with the parietal pericardium at the tracheal bifurcation and intimately adheres laterally to the mediastinal pleura. This anatomical relationship explains the onset of pericardial pleural effusion or empyema due to the involvement of the fascia of the chest wall and of the pericardial and pleural cavity. In immunocompromised patients, transdiaphragmatic spread through the oesophageal hiatus or the vena cava foramen may also occur [5].

Epidemiology

DNM is an acute polymicrobial infection of the mediastinum originating from odontogenic, oropharyngeal and cervical infection; it is mostly seen in young male adults and around the third–fourth decade [34, 35]. Odontogenic infection involving the second and third molars accounts for

40–60% of reported cases followed by retropharyngeal abscess (14%) and peritonsillar abscess (11%) [36], even though a recent meta-analysis has documented an increase in patients' age and a shift from mainly odontogenic infections to predominantly pharyngeal over time [37].

Less common causes include cervical lymphadenitis (7%), traumatic endotracheal intubation (7%), clavicular osteomyelitis (7%), external trauma (5%), *i.v.* drug abuse, suppurative parotitis, tonsillitis, thyroiditis and Ludwig's angina [38–41].

Risk factors include diabetes, alcoholism, previous malignancy and immuno-incompetence, whereas age >70 years, poor oral hygiene, malnutrition and long-term steroid therapy are associated with poor prognosis [34]. Descending mediastinitis has been classified according to the degree of dissemination revealed by CT scan into focal and diffuse types [42]. In type I (focal type), the infection is limited to the superior mediastinum above the tracheal bifurcation. In type II (diffuse type), there are two subtypes. In subtype IIA, infection is located in the inferior anterior mediastinum, while in subtype II, the infectious process reaches the inferior posterior mediastinum.

Microbiology and pathology

Nowadays, oropharyngeal or odontogenic infections rarely lead to serious complications, but DNM may be a more common finding in developing countries with poor economic conditions, and lack of medical prevention and treatment of dental and oropharyngeal diseases.

Most of these infections are polymicrobial aerobic- and anaerobic-exemplifying oropharyngeal flora [5, 26, 43]. Therefore, the most commonly isolated aerobic bacteria are β-haemolytic *Streptococcus*, this finding being related to the fact that many diabetes mellitus cases are secondary to odontogenic infections [5, 34] of *S. aureus* and *Klebsiella pneumoniae. Peptostreptococcus, Prevotella, Bacteroides fragilis* and *Porphyromonas* are among the anaerobic bacteria reported. Other micro-organisms commonly found include *Fusobacterium, Streptococcus viridans, Serratia marcescens, Enterobacter, Neisseria, Pseudomonas aeruginosa, Escherichia coli, Veillonella* and *Actinomyces* [5, 7, 27, 32, 36, 44]. Infection by these pathogens can involve any of the mediastinal structures, causing physiological compromise by compression, bleeding or systemic sepsis, or a combination of these.

The high toxicity in DNM has been attributed to the synergy of anaerobic and aerobic bacteria *versus* the limited number of immune-competent cells in the cervical mediastinum. The anaerobic bacteria have a great affinity for the lipid constituents of cell membranes, thus leading to hydrolysis of muscle cells, erythrocytes and platelet cells. The lower tissue oxygenation (as present particularly in diabetes or immunodeficiency) enhances the virulence of anaerobic bacteria, thus favouring the spread of infection caused by these organisms. Moreover, bacterial growth is increased by bacterial enzymes, such as fibrinolysin and coagulase (leading to tissue ischaemia), hyaluronidases, proteases and collagenases, that alter tissue constituents and fragment the support structures [43–45]. The tissue destruction is explained by an early multiple small-vessel obliterative vasculitis and thrombosis at the borders of the infectious focus that cause hypoxia, acute inflammation and extensive oedema of the subcutaneous fat layer [22]. Many authors postulate that the negative pressure in the mediastinum, gravity and respiration favour downward spread of infection along the cervico-mediastinal fascial spaces and planes and along the three layers of the deep cervical fascia [22, 27, 34]. As poor vascularisation, loose areolar tissue and shortage of cell defences are typical features of cervico-mediastinal spaces, each of these pathways is connected to pericardium, pleura and mediastinum, thus acting as a gateway for any oropharyngeal infection to the chest [22]. The evolution of the process will lead to decreased mobility of the mediastinal structures and development of dead space under the sternum.

Clinical findings

The wide clinical spectrum of DNM ranges from subacute forms to devastating patterns that warrant immediate intensive care [33]. The vagueness of early symptoms implicating mediastinal

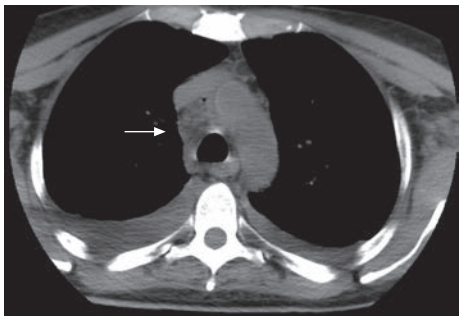


Figure 2. Descending necrotising mediastinitis. Computed tomography scan shows involvement of middle mediastinum (arrow) and initial bilateral pleural effusion.

involvement, the use of steroids reducing functional symptoms [46] and a clinician's lack of experience may cause delayed diagnosis [47–49], which has been appointed as a significant predictor of morbidity and mortality [37].

The early stage clinical pattern of DNM is completely nonspecific, and is characterised by signs and symptoms of sepsis, with stiffness, swelling and pain in the neck. The involvement of the mediastinum may occur as early as 12 h to or late as 2 weeks after infection, but most commonly it is seen within 24–48 h of the onset of the deep cervical infection and is manifested by chills, high-fever, tachycardia, dyspnoea and nonproductive cough. Pitting oedema and crepitation in the neck and upper anterior chest wall may be present associated with dysphagia, odynophagia, dysphonia, regurgitation and cervical skin oedema if a cervical abscess occurs. The involvement of the upper mediastinum elicits a retrosternal pain that radiates upwards into the neck, whereas an interscapular pain radiating around the chest is more suggestive of involvement of the posterior compartment of the inferior mediastinum. Pleural or pericardial involvement is indicated by friction rub and effusion. The retroperitoneal space of the abdomen may also be reached by the infectious process through the oesophageal hiatus. More advanced stages are characterised by sepsis and hypotension, decreased urine output and signs of tissue malperfusion, which inevitably result in a state of septic shock [36]. The crunching sound heard over the precordium during systole (Hamman's sign) is usually present, while cranial nerve deficit is common and is usually manifested by trismus [27].

Diagnosis

The diagnostic criteria for DNM have been clearly established by ESTRERA *et al.* [47] and include: 1) clinical evidence of severe oropharyngeal infection; 2) radiographic features of mediastinitis; 3) intra-operative or post-mortem documentation of necrotising mediastinal infection; and 4) establishment of a relationship between the oropharyngeal process and the DNM.

Conventional radiographic examination of the neck and chest may show retropharyngeal soft tissue swelling, widening of the retrocervical space with or without an air–fluid level, widening of the upper mediastinum (fig. 1), anterior displacement of the tracheal air column, mediastinal emphysema and loss of the normal lordosis of the cervical spine, although all of these signs are of limited sensitivity [9, 50].

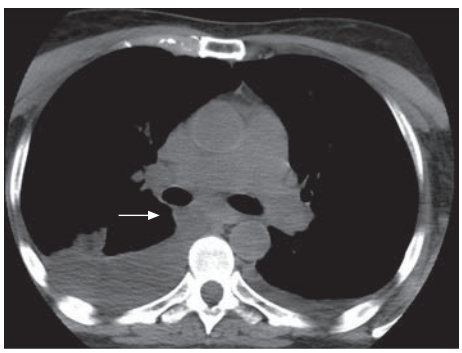


Figure 3. Descending necrotising mediastinitis. Computed tomography scan showing involvement of subcarinal and posterior mediastinum (arrow) with bilateral pleural effusion.

CT findings include abscess formation, soft tissue infiltration with loss of the normal fat planes, the absence of prominent lymphadenopathy and the presence of gas bubbles [51]. The scan is helpful in determining the downward extent of the inflammatory process, especially in the middle mediastinum and below the fourth thoracic vertebra, at the level of the carina (figs 2 and 3). Pleural and pericardial effusion may also be demonstrated (fig. 4). CT examination is recommended for every patient with a deep cervical infection so that the presence of DNM can be identified and anatomical changes identified (fig. 5). Contiguous, 1-cm cervicothoracic scans detail the continuity of the infection between the neck and the chest, establishing

the close relationship between neck infection and mediastinitis that can be easily detected (fig. 6) [5, 36, 48, 52–56].

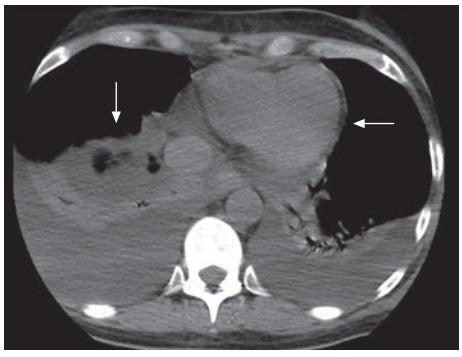


Figure 4. Descending necrotising mediastinitis. Computed tomography scan showing massive bilateral pleural effusion, lung atelectasis and pericarditis (arrows).

Treatment

Although its incidence is low, DNM is a real life-threatening disease, which dictates prompt combined medical and surgical treatment. Wide-spectrum *i.v.* antibiotics, intensive care and airway treatment should strictly complement surgical debridement of the oropharyngeal primary site of infection. The further surgical approach depends on the cause and extent of the infection, and the additional spaces involved. Mediastinal drainage is crucial to prevent any major damage and many types of procedures have been described, such as transcervical mediastinal drainage, video-assisted mediastinoscopy (VAM), anterior cervical mediastinotomy, median sternotomy, subxyphoid approach, clamshell incision and standard transthoracic procedures, such as posterolateral or anterolateral thoracotomy up to the more recent application of video-assisted thoracoscopic surgery (VATS) drainage. The choice of surgical approach is based on the extension of the infected area, the patient's performance status, the surgeon's personal experience, the severity of complications if present and the evolution of the disease, but is also determined by CT assessment [57]. The rarity of the disease itself makes it difficult to investigate, in a prospective fashion, the best approach [58].

The frequently used Endo's classification [42, 59–61] helps in establishing the most suitable access to accomplish a careful drainage of the infected area. Transcervical drainage, either open or by VAM and anterior cervical mediastinotomy are generally sufficient if the infection has not spread downward below the fourth thoracic vertebra, as in DNM type I (fig. 7) [22, 42, 62, 63]. However, due to the quick spread of such infection, some authors recommend direct mediastinal exploration without taking into consideration the level of involvement [58, 64–66]. If there is a concomitant pleural effusion, a percutaneous chest drain should be applied, whilst keeping in mind that soft rubber tissue drains should be used to avoid the erosion of a major arterial vessel in the mediastinal area. When the infection is confined to the anterior and inferior mediastinal compartment (DNM type IIA), in addition to the transcervical drainage, subxyphoid drainage of the anterior space may be satisfactory to ensure adequate drainage [42], but as an alternative, a midline sternotomy is a suitable, wide and easy access through which to accomplish a thorough debridement of the anterior mediastinum [44, 54]. Both the cervical and mediastinal wounds may be successfully sealed with the aid of vacuum-assisted closure device (V.A.C. Therapy System; KCI, San Antonio, TX, USA) [67, 68], which also provides continuous debridement of the area (fig. 8).

Figure 5. Descending necrotising mediastinitis. Coronal computed tomography scan showing air–fluid collection in parapharyngeal that involves left carotid sheath (arrow).

When the inflammatory process is below the fourth thoracic vertebra and extends to the lower posterior mediastinum (DNM type IIB), drainage of mediastinum must be necessarily accomplished by standard

Figure 6. Descending necrotising mediastinitis. Sagittal computed tomography scan showing extension of the infection in the retrocricoid area, paratracheal and pre-vertebral space.

posterolateral thoracotomy that provides optimal access to all mediastinal compartments, thus enabling careful debridement of purulent material and necrotic tissue at a minimal cost of morbidity, even in immunocompromised patients [5, 24, 48, 54, 58, 69, 70]. A successful trans-sternal and transpericardial approach has also been reported to reach a posterior mediastinal site of infection [71]. Bilateral empyema may require a different access, such as clamshell incision, that offers a one-step debridement of both chest cavities and mediastinal area, as experienced by many authors [37, 72, 73]. Nevertheless, it should be kept in mind that a more aggressive approach in these debilitated patients might increase morbidity and mortality [74, 75] and, last but not least, the potential bilateral excision of internal mammary arteries that will not be available for further CABG [76].

A feasible alternative to standard thoracotomy is VATS, which is particularly indicated in the early stages of the disease and provides a better mediastinal drainage compared with cervical drainage [74–80] without repositioning of the patient [62]. The main drawbacks are the difficulty in identifying collection of fluids, not to be misinterpreted with major vessels because of adhesion and engorgement due to inflammation, and inadequacy of debridement of extensive necrotising cellulitis, which is typical of diffuse DNM [24]. In patients with poor respiratory status, veno-venous extracorporeal membrane oxygenation has been suggested for use as a gas exchange support [81]. Post-operative care is multidisciplinary. The patient should be transferred to an intensive care unit where control of the airway should be performed, if necessary by tracheostomy, and treatment with high-dose *i.v.* broad-spectrum aerobic and anaerobic antibiotics immediately established, with further adjustment based on microbiology [34]. Some authors have suggested the use of adjuvant hyperbaric oxygen therapy for its bactericidal effect, activation of leukocytes and angiogenesis [73, 82, 83].

Figure 7. Descending necrotising mediastinitis following thyroid suppuration after fine needle aspiration. Cervical debridement has been accomplished and double-crossed cervical drainage put in place.

The first-ever reported large series in pre-antibiotic era documented mortality rates of 85% in conservatively treated patients and 35% in those approached by surgery [25]. The overall outcome of multidisciplinary treatment of DNM has changed over the last quarter of a century and, even though mortality rates of up to 83% have been reported, we have observed a general decrease of mean mortality even down to 0% in some instances (table 3). Therefore, a mortality rate >40% is unacceptable nowadays, provided that all possible measures are taken to prevent evolution towards septic shock [58, 84–92].

Subacute mediastinitis

Aetiology

The definition of subacute mediastinitis is unclear, but it should refer to inflammatory processes involving the mediastinum.

Pathology

Subacute infection is infrequently observed in previously healthy people, but it is becoming more common in immunocompromised patients, particularly those with AIDS. Mediastinal or hilar adenopathy is one of the dominant findings in almost two-thirds of AIDS patients with *Mycobacterium tuberculosis* infections, while atypical mycobacterial infection of the sternum and mediastinum may follow median sternotomy.

Figure 8. Descending necrotising mediastinitis successfully treated by cervical drainage and use of vacuum-assisted closure therapy.

Microbiology

Subacute infections are mostly attributable to histoplasmosis and to nontuberculous mycobacterial infection. Actinomycotic infections are rare.

Clinical findings

The inflammatory nature of the mediastinal mass is suggested by the CT pattern and is confirmed by gallium scintigraphy, especially in AIDS patients. Indium leukocyte scintigraphy may also be

Table 3. Meta-analysis of descending necrotising mediastinitis studies with at least 10 patients reported to date

First author [ref.]	Study period	Patients n	Surgical procedure n	LOS days	Survival outcome n/N	Mortality %
Chen [52]	1997–2007	18	C 10 VATS 6 VAM 1 Subxiphoid 1	40	15/18	17
Deu-Martìn [87]	1996–2006	43	C 8/T 35	39	34/43	21 1996–2000: 40 2001–2006: 4.3
Figueroa-Damian [88]	1996–1998	18	T 18	NA	9/18	50
Freeman [58]	1980–1998	10	T 10	46	10/10	0
Gawrychowski [84]	1995–2002	12	C 6/T 6	NA	2/12	83
Inoue [89]	1996–2004	13	C 6/T 5 VATS 2	46	12/13	8
Iwata [65]	1991–2003	10	T 10	62	8/10	20
Jarboui [90]	1986–2007	10	C 2/T 8	8	2/10	80
Karkas [53]	1995–2008	17	C 10/T 7	30	16/17	6
Kocher [37]	1999–2011	17	Sternotomy 8 Clamshell 9[#]	16	16/17	5.9[#]
Lanisnik [70]	1992–2006	17	C 5/T 12	44	16/17	6
Makeieff [23]	1984–1998	17	C 3/T 14	45	14/17	18
Marty-Ané [48]	1989–1999	12	C 1/T 11	NA	10/12	17
Misthos [54]	1985–2002	27	C 16/T 11	24	18/27	33
Nakamori [85]	1995–2002	11	C 5 Catheter 6	39	11/11	0
Pérez [91]	1990–2000	17	T 17	NA	10/17	41
Ridder [86]	1997–2008	45	None 1 C 39/T 5	36	40/45	11
Roccia [49]	1996–2005	23	C 8/T 15	32	16/23	30
Sumi [92]	1998–2005	14	Catheter 14	22	13/14	7

LOS: length of hospital stay; C: transcervical; VATS: video-assisted thoracoscopic surgery; VAM: video-assisted mediastinoscopy; T: transthoracic; NA: not available. [#]: one patient in septic shock died 2 days after surgery.

useful in identifying these subacute infections. The final diagnosis is made by identification of the specific organism by tissue stains or culture. Samples may be obtained by needle aspiration, or mediastinal exploration if necessary.

Treatment

Administration of targeted drug(s) for the specific organism identified is the gold standard. Although some organisms may show *in vitro* resistance to the anti-TB drugs, this treatment is usually successful. Whenever required, extensive completion debridement is useful.

Chronic fibrosing mediastinitis (mediastinal fibrosis and sclerosing mediastinitis)

Mediastinal fibrosis and the resulting clinical features are variously termed fibrosing mediastinitis, fibrous mediastinitis, sclerosing mediastinitis and granulomatous mediastinitis. Fibrosing mediastinitis is a rare condition characterised by the deposition of thick fibrous tissue encasing any of the various mediastinal structures outside the mediastinal lymph nodes. The process may involve and obstruct the major airways, central systemic veins, pulmonary arteries, pulmonary veins and the oesophagus. Fibrosing mediastinitis is often a progressive process and there are two different patterns of mediastinal involvement: focal or diffuse.

Aetiology and pathogenesis

Fibrosing mediastinitis may result from several factors, among which infection is the most common cause, in particular tubercular and fungal infections (table 4). Noninfectious causes include autoimmune diseases; Behçet's syndrome; sarcoidosis; rheumatic fever; neoplasms, such as Hodgkin's disease; radiation therapy; traumatic haemorrhage and drugs, particularly methysergide [93]. In rare occurrences, the disease is familial and multifocal, and patients may present different manifestations of the same disease, such as retroperitoneal and mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis and pseudotumour of the orbit [94]. Sometimes the lesion extends from the upper mediastinum to the soft tissue of the neck [9].

Table 4. Aetiology of sclerosing mediastinitis

Fungal infections
Histoplasmosis
Aspergillosis
Mucormycosis
Coccidioidosis
Cryptococcosis
Blastomycosis
Mycobacterial infections
Tuberculosis
Nontuberculous infections
Bacterial infections
Nocardiosis
Actinomycosis
Noninfectious
Autoimmune disease
Sarcoidosis
Rheumatic fever
Neoplasms (Hodgkin's disease)
Trauma
Drugs (methysergide)
Idiopathic
Familial multifocal
Retroperitoneal and mediastinal fibrosis
Sclerosing cholangitis
Riedel's thyroiditis
Pseudotumour of the orbit

The pathogenesis of extensive progressive fibrosis within the mediastinum remains under debate. Some authors have postulated that fibrosing mediastinitis results from a delayed hypersensitivity reaction to fungal or mycobacterial antigens from infected lymph nodes [95]. The presence of strongly positive skin and serum reactivity and hypergammaglobulinaemia and hypercomplementaemia support this theory.

Although *Histoplasma capsulatum* is the most common cause of fibrosing mediastinitis in the central United States, fibrosing mediastinitis affects only a small fraction of exposed individuals in endemic regions for histoplasmosis. This may be explained by an abnormal immunological reaction to *H. capsulatum* antigen rather than a direct infection.

Tuberculous mediastinitis is common in Turkey, and is probably due to rupture of diseased lymph

nodes or fibrocaseous granulomas in the neck and/or mediastinum. Mediastinal granuloma is the precursor lesion of mediastinal fibrosis. Rupture of a mediastinal granuloma releases antigens into the mediastinum, resulting in either localised or diffuse fibrosis [96].

Idiopathic fibrosing mediastinitis probably has a multifactorial pathogenesis for which both genetic and immunological factors are involved. It is characterised by three histological stages: stage I by oedema and fibromyxoid tissue, several spindle cells, eosinophils, mast cells, lymphocytes and plasma cells; stage II by thick glassy bands of randomly arranged collagen with focal interstitial spindle cells, lymphocytes and plasma cells; and stage III by by crowded acellular collagen and some calcification [97].

Pathology

Fibrosing mediastinitis is characterised by a diffuse, fibrotic infiltration of the mediastinal structures by chronic inflammatory cells. Mediastinal fibrosis leads to compression of airways, vessels and the oesophagus. The most common pattern is a mediastinal or hilar soft-tissue calcified mass, tissue planes are obscured, and the process may extend to involve the root of the lungs and the major pulmonary vessels. A much less common pattern is a diffuse homogeneous soft tissue extending throughout the mediastinum, more frequently without calcification. The first pattern generally follows histoplasmosis or TB while the diffuse distribution is typical of idiopathic or noninfectious fibrosing mediastinitis [98].

Clinical features

Fibrosing mediastinitis is more common in young adult white females, with a female-to-male ratio of 3:1, and may be self-limiting, but serious persistent complications can finally cause death. In ~40% of patients, the disease is asymptomatic and is an incidental radiographic finding. The clinical features are dictated by the compression and entrapment of visceral mediastinal structures that may cause superior vena cava syndrome, pulmonary hypertension, severe respiratory imbalance and dysphagia. Cough, dyspnoea, pleuritic chest pain, fever, weight loss, wheezing, post-obstructive pneumonia, dysphagia and haemoptysis are common. Hoarseness is due to compression of the left recurrent nerve with left vocal cord paralysis. Pulmonary interstitial fibrosis is a frequent complication and can mimic the clinical and pathological course of usual interstitial pneumonitis. A mediastinal subcarinal granulomatous disease may rarely lead to a broncho-oesophageal fistula.

Radiological findings

Fibrosing mediastinitis mostly manifests itself as nonspecific widening of the mediastinum with deformation and elimination of anatomical mediastinal profiles. Patients with superior vena cava obstruction may present a bilateral widening of the superior mediastinum due to engorged collateral veins, while atelectasis or recurrent pneumonia may be due to central airway involvement. Hilar and/or mediastinal lymphadenopathy with occasional calcifications may be detected on conventional radiographs, but no information is given on the site of lymph node involvement. Patients with major airway obstruction and disease in the subcarinal region may have normal radiographic findings. The mass, when present, is often asymmetric and commonly projects into the right hemithorax. CT examination in the limited form evaluates the impact of compression on the great arteries, trachea and oesophagus, usually showing a soft-tissue mass that most commonly infiltrates the middle mediastinum [97]. CT is more specific than a conventional radiograph or magnetic resonance imaging (MRI) in identifying any calcification in the lesion. MRI is crucial in assessing the mediastinal soft-tissue masses and outlines the extent of involvement of the great arteries, especially if the use of contrast material is contraindicated [99].

Radionuclide venography with technetium-99m to demonstrate occlusion of the vena cava is a quick and safe method of investigation. Pulmonary arteriography may be helpful when

involvement of the pulmonary vessels is suspected. Upper gastrointestinal contrast radiographic studies can demonstrate oesophageal narrowing. In the case of oesophageal involvement by fibrosing mediastinitis, a barium oesophagogram will typically show circumferential narrowing and long segment strictures without mucosal abnormality and the presence of mass effect. Angiography is the most exhaustive imaging technique with which to detect vascular involvement by fibrosing mediastinitis; it will be documented by long segment strictures and smooth stenosis in the vessels. Pulmonary arteriography and contrast venography are helpful in diagnosing pulmonary artery obstruction or superior vena cava stenosis [98].

Treatment

In vena caval obstruction, bypass of the obstructed superior vena cava by a vascular or prosthetic graft from the left innominate vein to atrium is indicated. Patients with pulmonary hypertension should be referred to a pulmonary hypertension centre, as there are no evidence-based therapeutic options. In ~25% of patients with localised granulomas, complete excision of the lesion can be achieved. When a broncho-oesophageal fistula is present, excision of the fistulous tract and closure of both the tracheal and oesophageal openings are required.

Conclusion

Mediastinitis is a rare though potentially life-threatening condition with an extremely high mortality rate if not promptly recognised and properly treated. The multifactorial aetiology, the ample clinical spectrum, a poor knowledge of the disease and the lack of prospective studies make it difficult to recognise the onset of the disease and establish the most appropriate treatment [100, 101]. Most cases are secondary to cardiovascular surgery and oesophageal perforation, but the most fatal expression is the DNM that originates from infectious foci in oropharyngeal cavity and spreads extensively *via* the mediastinum due to existing anatomical continuity through the neck [102]. The extent of infection, the diagnostic and therapeutic delay, and the septic shock at first observation directly affect morbidity and mortality, as recently reported [37].

Strong agreement exists among international experts regarding the best care of patients with severe sepsis and septic shock, which characterise the evolution of this disease [103]. This disease has to be detected as soon as possible and CT should be performed whenever symptoms of sepsis persist after treatment of oropharyngeal infections, especially in cases of retropharyngeal and parapharyngeal locations [51, 104, 105]. Nowadays, thanks to a multidisciplinary approach, the improvement of imaging techniques, the targeting of antibiotic therapy and the tailoring of surgical drainage procedures [106], the outcome has improved over the last 25 years and mortality rates have gone down from an astonishing 85% without treatment to almost 0% in properly treated cases.

Statement of Interest

H. Lode has been a Board member at Pfizer, Bayer Vaccines and Bayer Antibiotics. He has received fees for consultancy and payment for lectures from Pfizer, Bayer and 001.

References

1. Rupp ME. Mediastinitis. *In:* Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 6th Edn. New York, Elsevier/Churchill Livingstone, 2005; pp. 1070–1078.
2. El Oakley RM, Wright JE. Postoperative mediastinitis: classification and management. *Ann Thorac Surg* 1996; 61: 1030–1036.
3. Athanassiadi KA. Infections of the mediastinum. *Thorac Surg Clin* 2009; 19: 37–45.
4. Srirompotong S, Art-Smart T. Ludwig's angina: a clinical review. *Eur Arch Otorhinolaryngol* 2003; 260: 401–403.
5. Mihos P, Potaris K, Gakidis I, *et al.* Management of descending necrotizing mediastinitis. *J Oral Maxillofac Surg* 2004; 62: 966–972.

6. Ronson RS, Duarte I, Miller JI. Embryology and surgical anatomy of the mediastinum with clinical implications. *Surg Clin North Am* 2000; 80: 157–169.
7. Brook I, Frazier EH. Microbiology of mediastinitis. *Arch Intern Med* 1996; 156: 333–336.
8. Gardlung B, Bitover CY, Vaage J. Postoperative mediastinitis in cardiac surgery – microbiology and pathogenesis. *Eur J Cardiothorac Surg* 2002; 21: 825–830.
9. Akman C, Kantarci S, Cetinkaya S. Imaging in mediastinitis: a systematic review based on aetiology. *Clin Radiol* 2004; 59: 573–585.
10. Pinto A, Scaglione M, Scuderi MG, *et al.* Infections of the neck leading to descending necrotizing mediastinitis: role of multi-detector row computed tomography. *Eur J Radiol* 2008; 65: 389–394.
11. Exarhos DN, Malagari K, Tsatalou EG, *et al.* Acute mediastinitis: spectrum of computed tomography findings. *Eur Radiol* 2005; 15: 1569–1574.
12. Pate JW, Walker WA, Cole FH Jr, *et al.* Spontaneous rupture of the esophagus: a 30-year experience. *Ann Thorac Surg* 1989; 47: 689–692.
13. The Parisian Mediastinitis Study Group. Risk factors for deep sternal wound infection after sternotomy, a prospective, multicenter study. *J Thorac Cardiovasc Surg* 1996; 111: 1200–1207.
14. Loop FD, Lyte BW, Casgrve DM, *et al.* Sternal wound complications after isolated coronary bypass grafting; early and late mortality, morbidity, and cost of care. *Ann Thorac Surg* 1990; 49: 179–187.
15. Diez C, Koch D, Kuss O, *et al.* Risk factors for mediastinitis after cardiac surgery – a retrospective analysis of 1700 patients. *J Cardiothorac Surg* 2007; 2: 23.
16. Toumpoulis IK, Theakos N, Dunning J. Does bilateral internal thoracic artery harvest increase the risk of mediastinitis? *Interact Cardiovasc Thorac Surg* 2007; 6: 787–791.
17. Ang LB, Veloria EN, Evanina EY, *et al.* Mediastinitis and blood transfusion in cardiac surgery: a systematic review. *Heart Lung* 2012; 41: 255–263.
18. Curtis JJ, Clark NC, McKeney CA, *et al.* Tracheostomy. A risk factor for mediastinitis after cardiac operation. *Ann Thorac Surg* 2001; 72: 731–734.
19. Jolles H, Henry DA, Roberson JP, *et al.* Mediastinitis following median sternotomy: CT findings. *Radiology* 1996; 201: 463–466.
20. Weis F, Heyn J, Hinske CL, *et al.* Daptmycin as supportive treatment option in patients developing mediastinitis after open cardac surgery. *J Cardiothorac Surg* 2012; 7: 81.
21. Van Wingerteden J, Lapid O, Boonstra PW, *et al.* Muscle flaps or omental flap in the management of deep sterna wound infection. *Interact Cardiovasc Thorac Surg* 2011; 13: 179–188.
22. Sjögren J, Malmsjö M, Gustafsson R, *et al.* Poststernotomy mediastinitis: a review of conventional surgical treatments, vacuum-assisted closure therapy and presentation of the Lund University Hospital mediastinitis algorithm. *Eur J Cardiothorac Surg* 2006; 30: 898–905.
23. Makeieff M, Gresillon N, Berthet JP, *et al.* Management of descending necrotizing mediastinitis. *Laryngoscope* 2004; 114: 772–775.
24. Corsten MJ, Shamji FM, Frederico JA, *et al.* Optimal treatment of descending necrotising mediastinitis. *Thorax* 1997; 52: 702–708.
25. Pearse HE. Mediastinitis following cervical suppuration. *Ann Surg* 1938; 108: 588–611.
26. Smith JK, Armao DM, Specter BB, *et al.* Danger space infection: infection of the neck leading to descending necrotizing mediastinitis. *Emerg Radiol* 1999; 6: 129–132.
27. Kiernan PD, Hernandez A, Byrne WD, *et al.* Descending cervical mediastinitis. *Ann Thorac Surg* 1998; 65: 1483–1489.
28. Weaver E, Nguyen X, Brooks MA. Descending necrotising mediastinitis: two case reports and review of the literature. *Eur Resp Rev* 2010; 19: 141–149.
29. Mosher HP. The submaxillary fossa, approach to deep pus in the neck. *Trans Am Acad Ophtalmol Otolaryngol* 1929; 34: 19–26.
30. Beasley DJ, Amedee RG. Deep neck space infections. *J La State Med Soc* 1995; 147: 181–184.
31. Watanabe M, Ohshika Y, Aoki T, *et al.* Empyema and mediastinitis complicating retropharyngeal abscess. *Thorax* 1994; 49: 1179–1180.
32. Moncada R, Warpeha R, Pickleman J, *et al.* Mediastinitis from odontogenic and deep cervical infection. Anatomic pathways of propagation. *Chest* 1978; 73: 497–500.
33. Novellas S, Kechabtia K, Chevallier P, *et al.* Descending necrotizing mediastinitis: a rare pathology to keep in mind. *Clin Imaging*; 29: 138–140.
34. Cirino LM, Elias FM, Almeida JL. Descending mediastinitis: a review. *Sao Paulo Med J* 2006; 124: 285–290.
35. Ishinaga H, Otsu K, Sakaida H, *et al.* Descending necrotizing mediastinitis from deep neck infection. *Eur Arch Otorhinolaryngol* 2013; 270: 1463–1466.
36. Sancho LM, Minamoto H, Fernandez A, *et al.* Descending necrotizing mediastinitis: a retrospective surgical experience. *Eur J Cardiothorac Surg* 1999; 16: 200–205.
37. Kocher GJ, Hoksch B, Caversaccio M, *et al.* Diffuse descending necrotizing mediastinitis: surgical therapy and outcome in a single-centre series. *Eur J Cardiothorac Surg* 2012; 42: e66–e72.
38. Huang TT, Tseng FY, Liu C, *et al.* Deep neck infection in diabetic patients: comparison of clinical picture and outcomes with non-diabetic patients. *Otolaryngol Head Neck Surg* 2005; 132: 943–947.

39. Islam A, Oko M. Cervical necrotizing fasciitis and descending mediastinitis secondary to unilateral tonsillitis: a case report. *J Med Case Reports* 2008; 2: 368.
40. Iwama S, Kato Y, Nakayama S. Acute suppurative thyroiditis extending to descending necrotizing mediastinitis and pericarditis. *Thyroid* 2007; 3: 281–282.
41. Sarna T, Sengupta T, Miloro M, *et al.* Cervical necrotizing fasciitis with descending mediastinitis: literature review and case report. *J Oral Maxillofac Surg* 2012; 70: 1342–1350.
42. Endo S, Maruyama F, Hasegawa T, *et al.* Guideline of surgical management based on diffusion of descending necrotizing mediastinitis. *Jpn J Thorac Cardiovasc Surg* 1999; 47: 14–19.
43. Sandner A, Börgermann J, Kösling S, *et al.* Descending necrotizing mediastinitis: early detection and radical sugery are crucial. *J Oral Maxillofac Surg* 2007; 65: 794–800.
44. Sandner A, Börgermann J. Update on necrotizing mediastinitis: causes, approaches to management, and outcomes. *Curr Infect Dis Rep* 2011; 13: 278–286.
45. Ridder GJ, Technau-Ihling K, Sander A, *et al.* Spectrum and management of deep neck space infections: an 8-year experience of 234 cases. *Otolaryngol Head Neck Surg* 2005; 133: 709–714.
46. Eter EG, Khazzaka A, Mneimneh W, *et al.* Does diclofenac increase the risk of cervical necrotizing fasciitis in a rat model? *Int J Exp Pathol* 2009; 90: 58–65.
47. Estrera AS, Landay MJ, Grisham JM, *et al.* Descending necrotizing mediastinitis. *Surg Gynecol Obstet* 1983; 157: 545–552.
48. Marty-Ané CH, Berthet JP, Alric P, *et al.* Management of descending necrotizing mediastinitis: an aggressive treatment for an aggressive disease. *Ann Thorac Surg* 1999; 68: 212–217.
49. Roccia F, Pecorri GC, Oliaro A, *et al.* Ten years of descending necrotizing mediastinitis. Management of 23 cases. *J Oral Maxillofac Surg* 2007; 65: 1716–1724.
50. Cai XY, Zhang WJ, Zhang ZY, *et al.* Cervical infection with descending mediastinitis: a review of six cases. *Int J Oral Maxillofac Surg* 2006; 35: 1021–1025.
51. Gonzales-Garcia R, Risco-Rojas R, Roman-Romer L, *et al.* Descending necrotizing mediastinitis following dental extraction. Radiological features and surgical treatment considerations. *J Craniomaxillofac Surg* 2011; 39: 335–339.
52. Chen K, Chen J, Kuo S, *et al.* Descending necrotising mediastinitis: 10-year surgical experience in a single institution. *J Thorac Cardiovasc Surg* 2008; 136: 191–198.
53. Karkas A, Chahine K, Schmerber S, *et al.* Optimal treatment of cervical necrotizing fasciitis associated with descending necrotizing mediastinitis. *Br J Surg* 2010; 97: 609–615.
54. Misthos P, Katsaragakis S, Kakaris S, *et al.* Descending necrotizing anterior mediastinitis: analysis of survival and surgical treatment modalities. *J Oral Maxillofac Surg* 2007; 65: 635–639.
55. Scaglione M, Pinto A, Giovine S, *et al.* CT features of descending necrotizing mediastinitis – a pictorial essay. *Emerg Radiol* 2007; 14: 77–81.
56. Scaglione M, Pezullo MG, Pinto A, *et al.* Usefulness of multi detector row computed tomography in the assessment of the pathways of spreading of neck infections to the mediastinum. Semin Ultrasound CT MR 2009; 221–230.
57. Scaglione M, Pinto A, Romano S, *et al.* Determining optimum management of descending necrotizing mediastinitis with CT: experience with 32 cases. *Emerg Radiol* 2005; 11: 275–280.
58. Freeman RK, Vallieres E, Verrier ED, *et al.* Descending necrotizing mediastinitis: an analysis of the effects of serial surgical debridement on patient mortality. *J Thorac Cardiovasc Surg* 2000; 1119: 260–267.
59. Hasegawa T, Endo S, Sohara Y. Classification of descending necrotizing mediastinitis. *Ann Thorac Surg* 2000; 69: 1296.
60. Kim JT, Kim LH, Lee SW, *et al.* Descending necrotizing mediastinitis: mediastinal drainage with or without thoracotomy. *Thorac Cardiovasc Surg.* 1999; 47: 333–335.
61. Moriwaki Y, Sugiyama M, Matsuda G, *et al.* Approach for drainage of descending necrotizing mediastinitis on the basis of the extending progression from deep neck infection to mediastinitis. *J Trauma* 2002; 53: 112–116.
62. Min H, Choi YS, Shin YM, *et al.* Descending necrotizing mediastinitis. A minimally invasive approach using video-assisted thoracoscopic surgery. *Ann Thorac Surg* 2004; 77: 306–310.
63. Shimizu K, Otani Y, Nakano T, *et al.* Successful video-assisted mediastinoscopic drainage of descending necrotizing mediastinitis. *Ann Thorac Surg* 2006; 81: 2279–2281.
64. Casanova J, Bastos P, Barreiros F, *et al.* Descending necrotising mediastinitis – successful treatment using a radical approach. *Eur J Cardiothorac Surg* 1997; 12: 494–496.
65. Iwata T, Sekine Y, Shibuya K, *et al.* Early open thoracotomy and mediastinopleural irrigation for severe descending necrotizing mediastinitis. *Eur J Cardiothoracic Surg* 2005; 28: 384–388.
66. Wheatley MJ, Stirling MC, Kirs MM, *et al.* Descending necrotizing mediastinitis: transcervical drainage is not enough. *Ann Thorac Surg* 1990; 49: 780–784.
67. Domkowski PW, Smith ML, Gonyon DL, *et al.* Evaluation of vacuum-assisted closure in the treatment of poststernotomy mediastinitis. *J Thorac Cardiovasc Surg* 2003; 126: 386–390.
68. Gorlitzer M, Grabewoeger M, Meinhart J, *et al.* Descending necrotizing mediastinitis treated with rapid sternotomy followed by vacuum-assisted therapy. *Ann Thorac Surg* 2007; 83: 393–396.

69. De Freitas RP, Fahy CP, Brooker DS, *et al.* Descending necrotising mediastinitis: a safe treatment algorithm. *Eur Arch Otorhinolaryngol* 2007; 264: 181–187.
70. Lanisnik B, Cizmarevic B. Necrotizing fasciitis of he head and neck: 34 cases of a single institution experience. *Eur Arch Otorhinolaryngol* 2010; 267: 415–421.
71. Stella F, Petrella F. Transternal transpericardial approach for acute descending necrotizing mediastinitis. *J Thorac Cardiovasc Surg* 2005; 129: 212–214.
72. Ris H, Banic A, Furrer M, *et al.* Descending necrotizing mediastinitis: surgical treatment *via* clamshell approach. *Ann Thorac Surg* 1996; 62: 1650–1654.
73. Watanabe S, Kariatsumari K, Sakasegawa K, *et al.* A new combined surgical procedure for severe descending necrotizing mediastinitis with bilateral empyema. *Thorac Cardivasc Surg* 2002; 50: 308–310.
74. Cho JS, Kim YD, Hoseok I, *et al.* Treatment of mediastinitis using video-assisted thoracoscopic surgery. *Eur J Cardiothorac Surg* 2008; 34: 520–524.
75. Nagayasu T, Akamine S, Oka T, *et al.* Thoracoscopic drainage with wound edge protector for descending necrotizing mediastinitis. *Interact Cardiovasc Thorac Surg.* 2003; 2: 58–60.
76. Hirai S, Hamanaka Y, Mitsui N, *et al.* Surgical treatment of virulent descending necrotizing mediastinitis. *Ann Thorac Cardiovasc Surg.* 2004; 10: 34–38.
77. Isowa N, Yamada T, Kijima T, *et al.* Successful thoracoscopic debridement of descending necrotizing mediastinitis. *Ann Thorac Surg* 2004; 77: 1834–1837.
78. Nakamura Y, Matsumura A, Katsura H, *et al.* Successful videothoracoscopic drainage for descending necrotizing mediastinitis. *Gen Thorac Cardiovasc Surg* 2009; 57: 111–115.
79. Roberts JR, Smythe WR, Weber RW, *et al.* Thoracoscopic management of descending necrotizing mediastinitis. *Chest* 1997; 112: 820–854.
80. Son HS, Cho JH, Park SM, *et al.* Management of descending necrotizing mediastinitis using minimally invasive video-assisted thoracoscopic surgery. *Surg Laparosc Endosc Percutan Tech* 2006; 16: 379–382.
81. Murawaka T, Yshida Y, Fukami T, *et al.* Life-threatening tracheal perforation secondary to descending necrotizing mediastinitis. *Interact Cardiovasc Thorac Surg* 2010; 10: 454–456.
82. Flanagan CE, Daramola OO, Maisel RH, *et al.* Surgical debridement and adjunctive hyperbaric oxygen in cervical necrotizing fasciitis. *Otolaryngol Head Neck Surg* 2009; 140: 730–734.
83. Jallali N, Withey S, Butler PE. Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg* 2005; 189: 462–466.
84. Gawrychowski J, Rokicki W, Rokicki M. [Descending necrotic mediastinitis course and methods of surgical treatment.] *Pneumol Alergol Pol* 2003; 71: 17–23.
85. Nakamori Y, Fujimi S, Ogura H, *et al.* Conventional open surgery *versus* percutaneous catheter drainage in the treatment of cervical necrotizing fasciitis and descending necrotizing mediastinitis. *AJR Am J Roentgenol* 2004; 182: 1443–1449.
86. Ridder GJ, Maier W, Kinzer S, *et al.* Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. *Ann Surg* 2010; 251: 528–534.
87. Deu-Martìn M, Saez-Barb M, Lopez Sanz I, *et al.* Mortality risk factors in descending necrotising mediastinitis. *Arch Bronconeumol* 2010; 46: 182–187.
88. Figueroa-Damian R. Clinical manifestations and lethality of descending necrotizing mediastinitis. *Rev Invest Clin* 2001; 53: 35–40.
89. Inoue Y, Gika M, Nozawa K, *et al.* Optimum drainage method in descending necrotizing mediastinitis. *Interact Cardiovasc Thorac Surg* 2005; 4: 189–192.
90. Jarboui S, Jerraya H, Moussi A, *et al.* Descending necrotizing mediastinitis of odontogenic origin. *Tunis Med* 2009; 87: 770–775.
91. Pérez A, Cueto G, de la Escosura G, *et al.* Descending necrotizing mediastinitis. Results of medical-surgical treatment in 17 cases. *Gac Med Mex* 2003; 139: 19–204.
92. Sumi Y, Ogura H, Nakamori Y, *et al.* Nonoperative catheter management for cervical necrotizing fasciitis with and without descending necrotizing mediastinitis. *Arch Otolaryngol Head Neck Surg* 2008; 134: 750–756.
93. Mole TM, Glover J, Shepard MN. Sclerosing mediastinitis: a report on 18 cases. *Thorax* 1995; 50: 280–283.
94. Comings DE, Skubi KB, Van Eyes J, *et al.* Familial fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Reidel's thryoiditis and pseudotumour of the orbit may be different manifestations of a single disease. *Ann Intern Med* 1967; 66: 884–892.
95. Goodwin RA, Mickell JA, Des Prez RM. Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. *Medicine* 1972; 51: 227–246.
96. Kim HY, Song KS, Go JM, *et al.* Thoracic sequelae and complications of tuberculosis. *RadioGraphics* 2001; 21: 839–858.
97. Flieder DB, Suster S, Moran CA. Idiopathic fibroinflammatory (fibrosing/sclerosing) lesions of the mediastinum: a study of 30 cases with emphasis on morphologic heterogeneity. *Mod Pathol* 1999; 12: 257–264.
98. Rossi SE, McAdams HP, Rosado-de-Christenson ML, *et al.* Fibrosing mediastinitis. *Radiographics* 2001; 21: 737–757.
99. Rodriguez E, Soler R, Pombo F, *et al.* Fibrosing mediastinitis: CT and MR findings. *Clin Radiol* 1998; 53: 907–910.

100. Friedman BC, Pickul DC. Acute mediastinitis. What to do when the cause is nonsurgical. *Postgrad Med* 1990; 87: 273–275, 278–280, 285.
101. Karnath B, Siddiqi A. Acute mediastinal widening. *South Med J* 2002; 95: 1222–1225.
102. Wang LF, Kuo WR, Tsai SM, *et al.* Characterizations of life-threatening deep cervical space infections. A review of one hundred ninety-six cases. *Am J Otlaryngol* 2003; 24: 111–117.
103. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock 2012. *Crit Care Med* 2013; 41: 580–637.
104. Becker M, Zbaren P, Hermans R, *et al.* Necrotizing fasciitis of the head and neck: role of CT in diagnosis and management. *Radiology 197*, 202: 471–476.
105. Garcia T, Rios M, Paiva JA. Predictors of severity in deep neck infections admitted to the intensive care unit. *Anaesth Intens Care* 2012; 40: 832–837.
106. Singhal P, Kejriwal N, Lin Z, *et al.* Optimal surgical management of descending necrotising mediastinitis: our experience and review of literature. *Heart Lung Circ* 2008; 17: 124–128.

Chapter 12

Surgical management of pleural empyema

Michel Gonzalez[*], *Hans-Beat Ris*[*] *and Danail Petrov*[#]

SUMMARY: Pleural empyema has been classified into three different stages in order to facilitate the establishment of treatment guidelines. The treatment, which may range from conservative measures to more aggressive surgical management, depends on the chronicity of the empyema, the underlying disease and the condition of the patient. In this chapter, we review the different surgical options, with emphasis on the thoracoscopic management, which are now routinely performed for early-stage empyema. For advanced empyema, decortication is mandatory to prevent pulmonary restriction. Thoracoplasty or thoracostomy are reserved for special kinds of empyema.

[*]Thoracic Surgery Division, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.
[#]Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases, Medical University, Sofia, Bulgaria.

Correspondence: M. Gonzalez, Thoracic Surgery Division, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon, 1011 Lausanne, Switzerland.
Email: Michel.Gonzalez@chuv.ch

Eur Respir Monogr 2013; 61: 141–152.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041512
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The word "empyema" is derived from the Greek verb empyein ("to suppurate") and pleural empyema is, therefore, a suppurative disease of the pleura. Pleural empyema may be caused by various underlying conditions, which should be recognised, as the underlying condition influences the treatment strategy. Empyemas are generally due to pneumonia, which occurs in 20% to 57% of hospitalised patients [1–4]. Only 10% of patients with parapneumonic effusions will require a surgical management of their empyema [5]. However, misdiagnosis of this condition may lead to severe and disabling consequences, such as thoracic cavity deformation or scoliosis and pulmonary restriction. Empyemas are more common in males, with a male to female ratio of approximately 2:1. It is also more common in both extremes of age (children and elderly people). In most patients, associated risk factors for empyema development are found, including immunosuppressive conditions (HIV, diabetes mellitus, chronic renal failure, malnutrition and chemotherapy), alcohol, drug abuse, gastro-oesophageal reflux, broncho-aspiration and chronic parenchyma lung diseases, such as chronic obstructive pulmonary disease or fibrosis [6, 7].

Although primary pleural infections exist, most cases are secondary to pneumonia, lung abscesses or bronchiectasis. Other causes of secondary pleural infections include recent thoracic surgery, diagnostic procedures involving the pleural space, trauma, oesophageal ruptures, transdiaphragmatic spread of intra-abdominal infections and bronchial obstructions (table 1). Primary pleural infections have also been described and are thought to be related to the haematogenous spread of micro-organisms originating from gingival and upper respiratory tract infections (in most cases, microbiological cultures yield oropharyngeal flora and anaerobes) or can be related to *Mycobacterium tuberculosis* infections.

In a case series of 328 consecutive patients undergoing surgery for empyema, the underlying causes of pleural space infection were pneumonia in 200 patients (61%), previous thoracic or abdominal operations in 52 patients (16%), chest trauma in 32 patients (10%), *M. tuberculosis* infection in 20

Table 1. Aetiology of pleural empyema

Parapneumonic effusion
Haematogenous spread into pleural space
Iatrogenic infection of the pleural space (punction)
Post-operative (lung, cardiac, abdominal, urological)
Descending oropharynx infection
Mediastinal infection (oesophageal perforation)
Chest wall and spine infection
Post-traumatic penetrating injury

patients (6%), pulmonary embolism in 13 patients (4%), intrathoracic malignancies in five patients (2%), pleural aspergillosis in five patients (2%) and pleural actinomycosis in one patient (0.3%) [8].

Management

Principles

The choice of the appropriate intervention for pleural infection depends on the nature of the underlying disease, the chronicity of the empyema, the presence of a bronchopleural fistula (BPF) and the patient's overall condition. The management may range from noninvasive techniques, such as simple thoracentesis, chest tube drainage and intrapleural fibrinolytic therapies, to more invasive procedures, such as thoracoscopy, thoracotomy, open-window thoracostomy drainage or thoracomyoplasty (table 2).

The American Thoracic Society (ATS) has suggested classifying empyema into three different stages according to its chronicity in order to facilitate the establishment of treatment guidelines (table 3) [9]. Chest computed tomography (CT) scan is of importance in estimating the chronicity of empyema and detecting its underlying cause.

ATS stage I parapneumonic effusions are usually treated with antibiotics and thoracocentesis or chest tube drainage. Treatment of stage II empyema consists of fibrinolysis *via* chest tube or video-assisted thoracoscopic surgery (VATS) debridement. VATS is preferred in low-risk patients while fibrinolysis is an excellent option in patients who do not tolerate surgery. Fibrinolysis and VATS are valid options in the treatment of fibrinopurulent empyema, but they are not effective in its organising stage. Stage III empyema requires formal decortication in order to prevent recurrence and restriction.

Stage I

Stage I parapneumonic effusions are characterised by nonloculated effusion and are usually treated by antibiotics and thoracocentesis or chest-tube drainage.

Antibiotics

Once the pleural infection is diagnosed, antibiotics should be started based on the empirical pneumonia treatment guidelines and adapted on the pleural fluid cultures [10, 11]. All antibiotics penetrate the pleural space [12], with the exception of aminoglycosides, which may be deactivated by the low pleural pH fluid in cases of empyema [13]. Bacteria responsible for pleural empyema differ between community-acquired and hospital-acquired infections. In 2005, MASKELL *et al.* [14] have reported the microbiological findings in 430 patients with empyema. Pleural fluid culture was positive in 32 (54%) patients. The micro-organisms cultivated were *Streptococcus milleri* (29%), *Streptococcus pneumoniae* (16%), *Staphylococcus aureus* (21%) and anaerobes (15%). In addition, LUH *et al.* [15] reported in 2005 pleural cultures were positive in 178 (76%) out of 234 patients. Micro-organisms cultivated were *S. pneumoniae* (20%), *S. aureus* (21%), coagulase-negative *Staphylococcus* (17%), *Pseudomonas* (14%) and *Klebsiella* (10%).

Table 2. Options for the treatment of pleural empyema

Antibiotics
Thoracocentesis, chest tube
Fibrinolysis
Video-assisted thoracoscopic surgery debridement
Decortication
Myoplasty (intrathoracic muscle transfer)
Thoracomyoplasty
Open-window thoracostomy (pleurostomy)

There are numerous antibiotic combination regimens [10]. In community-acquired infections, intravenous amoxicillin and clavulanic acid or a combination of a second

Table 3. Characteristics of parapneumonic effusions according to American Thoracic Society (ATS) staging

	ATS stage I (exudative)	ATS stage II (fibrino-purulent)	ATS stage III (organising)
Pleura	Thin	Fibrin deposition/loculi	Thick
Fluid appearance	Clear	Opalescent	Frank pus
Bacteria	Sterile	Positive	Positive
pH	>7.20	<7.20	<7.20
Lactate dehydrogenase UI·L^{-1}	<500	>1000	>1000
Glucose mg·dL^{-1}	>60	<60	<60

generation cephalosporin and metronidazol is generally recommended against expected micro-organisms (*Pneumococcus*, *S. aureus* and *Haemophilus influenzae*) (table 4). The alternative for patients with β-lactam allergy is monotherapy of clindamycine. Gram-negative micro-organisms should be also treated in hospital-acquired empyemas, including carbapenem, piperacillin/tazobactam or third/fourth-generation cephalosporins (ceftazidime and cefepime) with metronidazole. Vancomycin should be added for suspected or proven methicillin-resistant *S. aureus*.

Antibiotic treatment duration for pleural infection without surgery remains controversial. Several weeks of antibiotherapy have been recommended in situations of empyema associated with a pulmonary disease (*i.e.* lung abscess) [16, 17]. If adequate pleural drainage is achieved, 3 weeks of *i.v.* antibiotherapy administration is generally performed followed by 3 weeks of oral antibiotherapy [10].

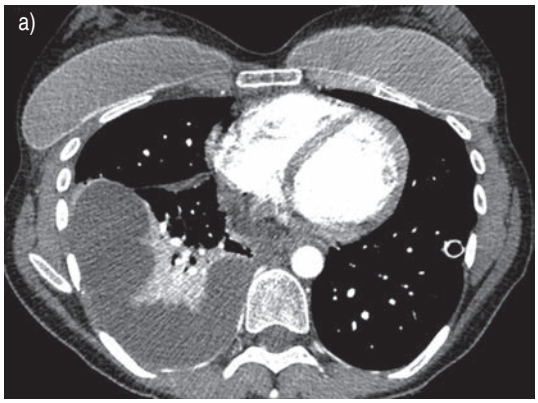
Drainage

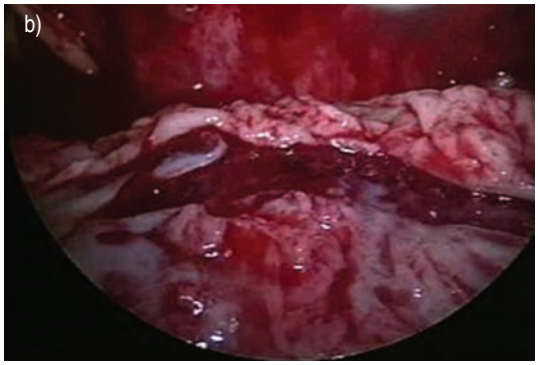
When fluid has been detected by radiological imaging, thoracentesis should be performed initially. Parapneumonic effusions should require a drainage procedure in the presence of the following criteria: 1) pleural effusion size >10 mm; 2) pH <7.20; 3) purulent pleural fluid; 4) radiological loculations; and 5) Gram-positive stain [18]. There is no consensus on the size of the optimal chest tube drainage [19–26]. Traditionally, chest tube drainage is performed using a large (24–28 French) intercostal drain positioned in the dependent part of the free-flowing pleural fluid because some authors consider large chest tubes more efficient for drainage of thick pus. However, adhesions and loculations may complicate chest tube insertion and it is generally recommended to insert a smaller catheter (10–14 French) using the Seldinger technique under ultrasound or CT-scan guidance in these situations [27]. These small drains are less traumatic to insert and better tolerated by patients. RAHMAN *et al.* [28] has reported a prospective, controlled, nonrandomised multicentre study of 405 patients treated for parapneumonic effusions and empyema with different chest tube sizes. Smaller wire-guided chest tube insertion caused significantly less pain than larger tubes with no difference in the clinical outcome for the management of complicated pleural effusions. There is also no consensus with respect to the force and type of the suction, the tube setting and specification of system used.

Table 4. Antibiotic regimen for initial treatment

Origin of infection	*i.v.* treatment	Oral treatment
Community-acquired	Cefuroxime + metrodinazole	Amoxicillin + clavulanic acid
	Benzyl-penicillin + ciprofloxacin	Amoxicillin + metronidazole
	Meropenem + metronidazole	Clindamycin
Hospital-acquired	Piperacillin + tazobactam	Not applicable
	Ceftadizime	Meropenem + metronidazole

Reproduced from [10] with permission from the publisher.





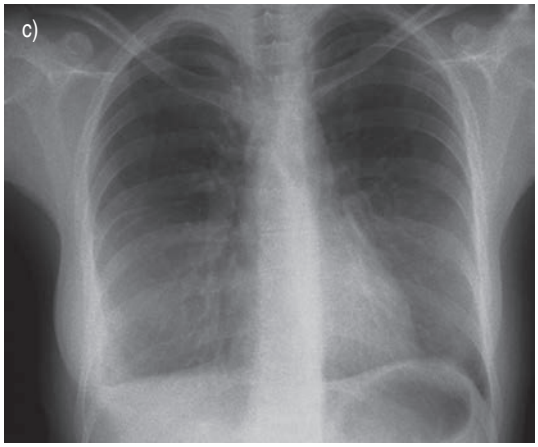


Figure 1. a) Empyema stage II with loculations. b) The patient underwent successful video-assisted thoracoscopic surgery debridement. Intra-operative view with fibrin deposits on visceral pleura, and c) post-operative chest radiograph.

Successful closed-tube drainage leads to the improvement of the clinical and radiological status within 24 h. Unsatisfactory pleural drainage can be due to the misplacement of the drain, the presence of loculations or the presence of a fibrous remodelling of the visceral pleura, which prevents lung re-expansion. If poor drainage persists, a CT scan should be performed to check for the drain position or the presence of additional loculations that are not in communication with the chest tube [29]. Chest tube tubes are generally left in place until the drainage rate is <50 mL per 24 h. Drainage performed as a single procedure is usually a first-line therapeutic modality with a success rate for post-pneumonic pleural empyema of between 67% and 74% [30], and with 36–65% failure rate for post-operative and post-traumatic empyema [31]. The mortality of pleural empyema treated by drainage ranges from 11% to 24% [30, 31]. In a prospective randomised study [32], tube thoracotomy for parapneumonic effusion has been compared with VATS debridement, and the authors found more conversion to open decortications for tube thoracostomy (37% *versus* 17%, $p<0.05$) and longer hospital stay (8.3 *versus* 12.8 days, $p<0.05$).

Stage II

Stage II empyema is characterised by the appearance of loculated effusion and intrapleural pH measurements of <7.2. The treatment options for this stage consist of the instillation of fibrinolytic agents or early debridement by VATS or thoracotomy (fig. 1).

Fibrinolytic therapy

In 1949, TILLET and SHERRY [33] described intrapleural fibrinolytic therapy with streptokinase and streptodornase through the chest tube to facilitate the drainage and prevent the development of loculations in patients with pleural effusions. Progressively, there have been several uncontrolled studies concluding that fibrinolytics were useful in the management of parapneumonic effusions, disrupting pleural loculations before deposition of collagen fibres and fibroblasts could occur (table 5) [6, 35–37]. Three types of fibrinolytics are principally used and have been well documented: streptokinase [38], urokinase [39] and tissue plasminogen activator (tPA) [40]. Streptokinase is generally administered as 250 000 units diluted into 20–100 mL of a saline solution. Urokinase is generally administered as 100 000 units diluted into 100 mL of saline solution. The fibrinolytic solution is injected into the pleural cavity *via* a chest tube drain, which is clamped for 2–4 h. Suction is then reapplied to the chest tube for the remaining 20–22 h. We favour one instillation of urokinase per day repeated during five subsequent days. A radiological control of the pleura and lung should

Table 5. Practical usage of intrapleural fibrinolytics

Fibrinolytic	Dose	Instillation	Duration
Streptokinase	250 000 IU	100–200 mL saline	Daily for up to 7 days
Urokinase	100 000 IU	100 mL saline	Daily for up to 3 days
Tissue plasminogen activator	10–25 mg	100 mL saline	Twice daily for up to 3 days

Reproduced from [34] with permission from the publisher.

then be performed. The expected adverse effects of fibrinolytics are localised pleural and systemic bleeding or acute respiratory distress syndrome [41–43].

The effectiveness of intrapleural fibrinolyticsis is still being debated in the literature. Clinical and radiological improvement of empyema with the use of fibrinolytics has been reported in several controlled studies [35, 44–52]. Small randomised controlled trials on fibrinolytic therapy have reported an improved radiological appearance [38, 39, 53], a better drainage of pleural fluid [37, 38, 53–55], a decreased hospital stay [38, 55] and a lesser need for surgery [39, 54, 56] in patients with empyema. A randomised control study of patients with mixed stages of empyema reported a significantly lower decortication rate (60 *versus* 29%, $p<0.01$) and shorter hospital stay in patients treated with intrapleural urokinase compared with sodium chloride instillation [56]. In contrast, a systematic review of the Cochrane library found no significant benefit for fibrinolytic therapy in empyema [57]. The Multicenter Intrapleural Sepsis Trial (MIST)-1 was the largest trial to be carried out in the United Kingdom [14], involving 454 patients, and was published in 2005. The MIST-1 studied the utility of fibrinolytics therapy in 454 patients with parapneumonic effusion with randomisation to receive streptokinase or sodium chloride instillation. There was no difference in mortality, the requirement of surgery in patients, the radiological outcome and the length of hospitalisation. This trial was criticised for its lack of consistency in the treatment protocols, the use of small tube drainage and the lack of clear outcomes regarding treatment failure with differences in the on-site surgical expertise. The message of this study was that there was no role for intrapleural fibrinolytics in late empyema. More recently, RAHMAN *et al.* [58] reported on a randomised trial including 210 patients with pleural infection treated with pleural instillation of sodium chloride, tPA, DNAse, or both tPA and DNAse. They found that intrapleural instillation of tPA and DNase together improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. In addition, the treatment with either DNase alone or tPA alone was ineffective compared with sodium chloride instillation.

In conclusion, current data suggests that intrapleural fibrinolytics may be considered for management of ATS stage II parapneumonic effusion and in high-risk patients who may not tolerate surgery with lung exclusion (for example, ventilated patients in the intensive care unit). However, intrapleural fibrinolytics cannot be recommended as the standard treatment of parapneumonic effusion and empyema and the use of fibrinolytics should not delay surgical intervention when appropriate.

Thoracoscopy

From the mid-1990s, thoracoscopic treatment of empyemas has gained in acceptance [59, 60]. Potential advantages of VATS include improved visualisation, less surgical trauma and improved quality-of-life outcomes. In this sense, VATS has been initially used in early-stage empyema to debride purulent collections and resect fibrin septae that fail to resolve with antibiotics and chest tube drainage (with or without fibrinolytic therapy). VATS has the advantage of being less invasive than open decortication and of being better accepted by the referring physician and the patient. Nowadays, early open decortication has been abandoned in many centres in favour of VATS debridement or fibrinolysis [15, 61–64]. Loculations may be broken down, the visible pleural space completely drained and the intercostal chest tube can be optimally placed. The VATS procedure is

intended to evacuate the fibrinous deposits and breakdown of loculations rather than peeling of organised pleura (VATS debridement) [65]. Several reports have demonstrated that VATS debridement is a valid treatment option for ATS stage II empyema that allows an appropriate control of infection and a complete restoration of pulmonary function in early-stage empyemas. Formal exclusion criteria for a primary VATS approach are suspicion of lung abscess, BPF, tumour at initial work-up or the need for muscle flaps with or without thoracoplasty [8, 61]. Presumed ATS stage III empyema with pleural thickening and signs of restriction on CT scan is no longer a formal contraindication, but the conversion rate to decortications *via* thoracotomy is high [61, 64].

We have used a standardised approach for VATS debridement [8, 66]. After a double-lumen intubation, the patient is installed in a lateral position. A 3-cm incision is performed in the ventral aspect of a traditional postero-lateral incision. Digital exploration is performed to assess the chronicity of the empyema and to dissect the pleural space. An optic 30° thoracoscope is placed above the first incision within the dissected area. No retractors are used and no rib spreading is involved. The chest cavity is then debrided and the lung freed circumferentially from the apex to the diaphragm. A third incision is performed in the sixth intercostal space to expose lung surface and fissure. The debridement of the visceral pleura and the fissures is performed using both sharp and blunt dissection avoiding parenchymal injury. The pleural cavity is then rinsed with several litres of warm saline solution and two 28 French chest tubes are finally inserted in the costodiaphragmatic sulcus and the pleural dome. Complete pulmonary re-expansion is controlled at the end of the procedure. The antibiotic regimen is discontinued 14 days after the operation and the chest tubes are removed in the absence of air leaks and when the drainage is <200 mL·day^{-1}.

In patients with ATS stage II empyema only, a small prospective randomised study of 20 patients [67] compared VATS debridement with streptokinase-based fibrinolytic therapy. The authors found that VATS was significantly better in controlling infection (91% *versus* 44%, $p<0.05$), limiting drainage duration (5.8 days *versus* 9.8 days, $p=0.03$), and decreased hospital stay (8.7 days *versus* 12.8 days, $p=0.009$). However, caution in the interpretation of these results is required as the sample size was small.

In studies for mixed stage (ATS stage II and III), the rate of conversion from VATS to open decortication ranges from 0% to 3.5% in early stage and from 7.1% to 59% in late stage [8, 15, 59, 61–64, 68, 69]. This discrepancy in the results emerging from these reports may be explained by differences in patient selection and interpretation in stage of their empyema. The higher conversion rates are related to chronic ATS stage III empyema, delays to surgery, presence of Gram-negative organisms and surgeon's experience. The failure of VATS, the persistence of empyema or insufficient pulmonary re-expansion requires further operations [70]. LUH *et al.* [15] reported this complication for 4.8% of those in the fibrinopurulent stage and 10% of those in the organised stage. Others have reported the incidence to be as high as 46% [8]. It is agreed that if adequate pulmonary re-expansion cannot be obtained during the VATS procedure, open thoracotomy should be performed during the same intervention to avoid re-operation and lung entrapment leading to late restriction [8]. *S. aureus* and *S. pneumoniae* [15, 71] were the most common organisms isolated. Also, the presence of Gram-negative organisms was an independent predictor of conversion from VATS to open decortication [8].

The benefits of a VATS procedure compared with thoracotomy are as follows: 1) a lower incidence of pulmonary complications, such as atelectasis, prolonged air leak, re-intubation and need for tracheostomy; 2) a lower pain score; and 3) shorter hospital stay. TONG *et al.* [60] have reported the outcome of 420 consecutive patients undergoing VATS or open decortication. Significantly fewer post-operative complications occurred in the VATS group for atelectasis, prolonged air leak, re-intubation, ventilator dependence, need for tracheostomy, blood transfusion, sepsis and 30-day mortality. CHAN *et al.* [62] demonstrated that intra-operative blood loss, duration of chest drain, length of hospital stay and post-operative complications were similar in the VATS and open decortication groups. The patients who benefited from the VATS approach reported significantly less post-operative pain ($p=0.04$), greater satisfaction with wounds ($p<0.0001$) and greater

satisfaction with the operation overall ($p=0.006$). Moreover, two studies compared VATS with open decortication in chronic empyema. A prospective cohort study [68] of 36 patients treated by VATS for multiloculated empyema showed a 58% success rate. Operating time and post-operative hospital stay was significantly longer in open decortication. CARDILLO *et al.* [63] reported the VATS approach in 185 patients in comparison with 123 open decortications. They found that the VATS approach showed statistically significantly better results in terms of in-hospital post-operative pain ($p<0.0001$), post-operative air leak ($p=0.004$), operative time ($p<0.0001$), hospital stay ($p=0.020$) and time to return to work ($p<0.0001$). In addition, re-operation for bleeding (4.8% *versus* 1%) and mortality (3.2% *versus* 0%) were higher in open decortication than in VATS procedures. These different studies did not report precisely on the stage of empyema and the chronicity of the pleural infection.

The long-term results of debridement with VATS do not appear to differ significantly from those of thoracotomy. One prospective study [72], included 45 patients with pleural empyema. The success rate of VATS was 82%. At follow-up, 86% of the patients treated by VATS operation showed normal pulmonary functions value. 14% had a moderate obstruction and restriction without impairment of exercise capacity. In addition, SOLAINI *et al.* [64] reported 90% of positive results with forced expiratory volume in 1 s >90% predicted at 6 months' follow-up. Another report [65] showed some degree of restriction in ~30% of the patients undergoing VATS debridement at pulmonary function testing 6 months after operation.

In conclusion, VATS is now the first approach for empyema in early stage when tube thoracostomy fails or when there is a clear indication for surgery. VATS debridement offers equivalent outcomes in term of resolution of empyema in comparison with open decortications for early stage (stage II). Moreover, VATS decreases morbidity, post-operative respiratory complications and length of hospital stay. However, thoracotomy should be liberally used in case of non re-expanding lung or when an additional procedure is necessary, such as muscle flap or bronchopleural repair.

Stage III

ATS stage III parapneumonic empyema is characterised by loculated effusion with pleural enhancement and signs of restriction on CT scan associated with raised temperature, weight loss and elevated C-reactive protein levels (fig. 2). Decortication is mandatory to achieve permanent control of the infection by evacuating loculated pus and fibrin debris, and prevent late pulmonary restriction resulting from lung fibrous encasement by removing both parietal and visceral debris (peel) without injuring the lung. This technically demanding procedure is usually performed by thoracotomy or may be attempted by VATS in selected cases. If the lung is destroyed or not able to fill the cavity, thoracoplasty or open thoracic window in critically ill patients may be necessary.

Figure 2. American Thoracic Society stage III parapneumonic empyema with pleural enhancement and signs of restriction (narrowing of the intercostal spaces). Note the presence of pleural microbubbles that can be suggestive of anaerobic germ infection.

Thoracotomy

Decortication by thoracotomy is generally indicated in the management of stage III empyema, which is characterised by loculated effusion with pleural thickening and signs of pulmonary restriction on the chest CT scan. Also, in some patients, very quick encapsulation occurs so that localised liquid collections become inaccessible for thoracenthesis, especially if localised medially in the posterior parts

of the pleural cavity. Organisation of the peel from the underlying visceral pleura usually begins 2–3 weeks after the onset of infection. Formal decortication by thoracotomy with resection of rib 7 (Fowler–Delorme procedure) or without a rib resection is the only way to free the trapped lung and to prevent recurrence of infection and restriction [65]. Decortication relies on freeing the encased lung parenchyma from the compressing inflammatory coat and relying on its elasticity to fill the cavity. The basic principle for this procedure is to remove the peel both from the visceral and parietal surfaces. In addition, complete closure of BPF may be performed. Besides, costomediastinal and costodiaphragmatic sinuses should be liberated as much as possible in order to enable diaphragm motility and restore ventilatory function of the affected lung. There are two morphological types of stage III empyema determining the operative tactics. 1) In some patients, the expanded part of the lung covers the empyema sac, filling the apical part of the hemithorax, with an empyema sac reaching up to either the middle or two-thirds of the distance from the base to the apex. This is the more favourable situation in which the cleavage plane can be found more safely. 2) Another situation exists if the empyema sac covers the compressed lung with the insertion sometimes deep in the mediastinum. In this situation, extrapleural dissection should be performed cautiously in order to avoid injury of the great vessels.

In some patients, it is possible to remove the entire empyema sac. However, in most patients it is not possible and the lung must be liberated gradually, usually starting extrapleurally in the direction that is found to offer the most suitable cleavage plane, until the junction level with the untrapped lung is reached. Effort should be made to identify the aorta and oesophagus on the left, the azygo-caval junction on the right and the vascular structures of the apex by dissecting in the intrapleural plane. A small part of peel may be left just adjacent to the aorta, which is usually fully exposed. When the underlying lung cannot be expected to re-expand due to concomitant removal of the affected destroyed lung, an obliteration of the pleural space cavity is mandatory. The affected lung may be removed when the CT scan demonstrates cavitary disease, large cystic bronchiectasis or concomitant neoplasm. Residual pleural spaces after decortication may be managed with transposition of muscle flaps or with thoracoplasty, as described later.

A study showed the effect of decortication for chronic empyema on pulmonary perfusion in 26 patients before and 35 weeks after treatment [73]. A significant increase in lung perfusion was found after decortication from 25% to 45% on the right side and from 18% to 34% on the left side. The predicted vital capacity increased from 62% to 80%, forced expiratory volume in 1 s increased from 50% to 70% after decortication. Similar results were obtained by SWOBODA *et al.* [74]. However, if left untreated for long periods of time, chronic empyema may result in irreversible restriction and loss of pulmonary function. Therefore, pleural decortications should be performed as soon as possible after chronic empyema has been diagnosed.

Thoracomyoplasty

Thoracomyoplasty is a procedure to be used as a last resort, and consists of the subperiostal removal of a varying number of rib segments associated with myoplasty, thus allowing space obliteration in situations of infected pleural spaces after lung resection. Space obliteration is achieved by bringing the chest wall to the lung and by filling the pleural space with viable tissue. This procedure may also be used to close a BPF. De Cerenville (1845–1915) was the first to use thoracoplasty for collapse therapy in case of tuberculosis (TB) [75]. Since 1950, this indication disappeared progressively due to the advent of antituberculous drugs. Extra-periosteal limited tailored thoracomyoplasty, as described by Alexander [76], is still indicated for patients with chronically infected pleural spaces after lobectomy, with pleural aspergillosis with or without pulmonary resection and with post-pneumonectomy pleural aspergillosis and TB. In our institution, we performed 17 limited extraperiosteal apical thoracomyoplasties for patients with chronic post-lobectomy empyema and infected apical residual spaces (fig. 3) [76]. Thoracomyoplasty was successful in all patients with respect to infection control, space obliteration and definitive closure of BPF, irrespective of the type of infection, the presence of a BPF and whether a first rib resection was performed. Post-operative shoulder girdle dysfunction and scoliosis were prevented in most patients willing to undergo intense physiotherapy. These

results are consistent with three recent studies [77–79] on 76, 35 and 26 patients, respectively, which investigated thoracomyoplasty for chronic pleural suppurative infection with 90%, 100% and 77% successful infection control, respectively.

Thoracomyoplasty initially designed to control chronic tuberculous infections is therefore still a valid surgical option in the treatment of specific chronic post-resectional empyemas, particularly in immunocompromised patients with complex intrathoracic infections. It is also useful for the control of post-pneumonectomy BPF associated with active TB and pleural aspergillosis.

Open-window thoracostomy

Open-window thoracostomy may be necessary to control chronic pleural infection in debilitated patients who are not eligible for decortication or thoracoplasty. Thoracostomy may be either permanent or transitory [75, 80]. Transitory thoracostomy may be part of the treatment of post-pneumonectomy BPF. Permanent thoracostomy may be required in elderly patients with chronic post-TB empyema and calcifications. These patients are usually malnourished and have complex comorbidities, which preclude formal decortication. Surgical removal of these calcifications can be life-threatening as they can be associated with important bleeding and lead to important residual spaces. Therefore, these situations may require the creation of a permanent thoracic window, as first described by Eloesser [74]. The Eloesser flap, described in 1935, consists of the marsupialisation of the cavity with rib resection and open drainage. The cavity is then easily packed by gauze that is changed daily. Patients can tolerate open-window thoracostomy for a long time and with minimal sacrifice of normal daily activities. When the infection is controlled, the window may close spontaneously or muscle transposition may be performed to fill the pleural space.

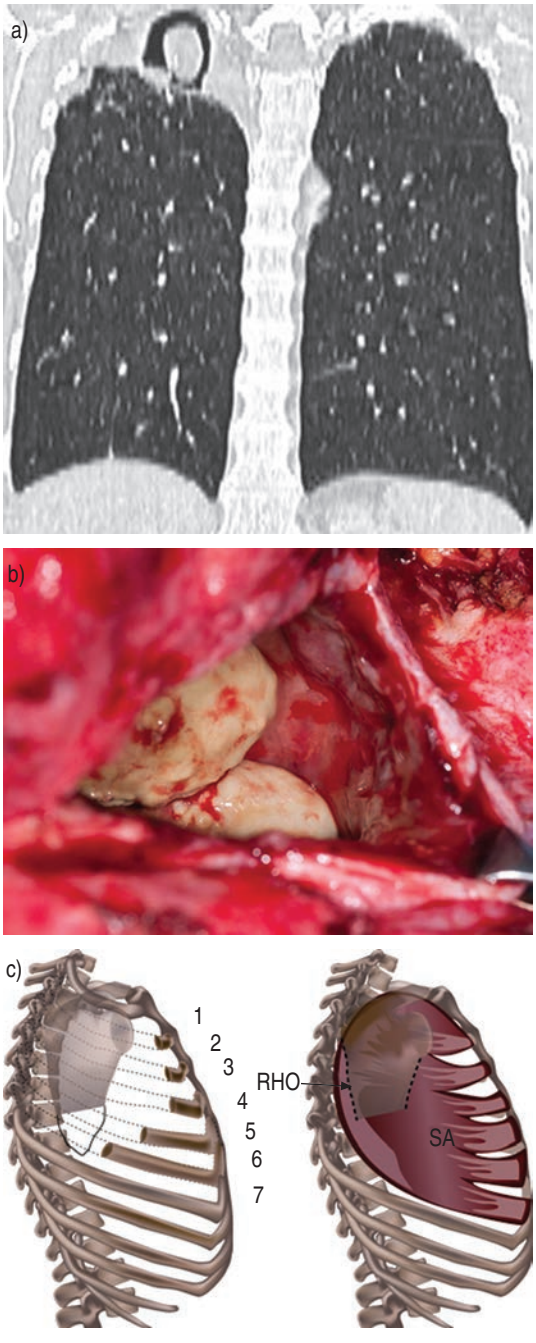


Figure 3. Pleural aspergillosis. a) Pre-operative chest computed tomography scan showing the cavity with the aspergilloma in the right pleural cavity, b) intra-operative view of the pleural aspergilloma, and c) schematic view of the limited apical thoracomyoplasty. RHO: rhomboideus; SA: serratus anterior. Reproduced from [76] with permission from the publisher.

Recently, we reported 27 patients who underwent iterative vacuum-assisted closure (VAC) therapy for the treatment of severe intrathoracic infections with or without lung resection [81]. The median length of VAC therapy was 22 days (range 5–66 days) and the median number of VAC changes per patient was 6 days (range 2 to 16 days). Control of intrathoracic infection and closure of the chest cavity was achieved in all surviving patients. VAC therapy seems to be an efficient and safe adjunct with which to treat

severe intrathoracic infections (especially for empyema post-pneumonectomy) and may be a good alternative to open-window thoracostomy in selected patients.

Statement of Interest

None declared.

References

1. Taryle DA, Potts DE, Sahn SA. The incidence and clinical correlates of parapneumonic effusions in pneumococcal pneumonia. *Chest* 1978; 74: 170–173.
2. Light RW, Girard WM, Jenkinson SG, *et al.* Parapneumonic effusions. *Am J Med* 1980; 69: 507–512.
3. Heffner JE, McDonald J, Barbieri C, *et al.* Management of parapneumonic effusions. An analysis of physician practice patterns. *Arch Surg* 1995; 130: 433–4338.
4. Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc* 2006; 3: 75–80.
5. Chapman SJ, Davies RJ. Recent advances in parapneumonic effusion and empyema. *Curr Opin Pulm Med* 2004; 10: 299–304.
6. Sahn SA. Management of complicated parapneumonic effusions. *Am Rev Respir Dis* 1993; 148: 813–817.
7. Ferguson AD, Prescott RJ, Selkon JB, *et al.* The clinical course and management of thoracic empyema. *QJM* 1996; 89: 285–289.
8. Lardinois D, Gock M, Pezzetta E, *et al.* Delayed referral and Gram-negative organisms increase the conversion thoracotomy rate in patients undergoing video-assisted thoracoscopic surgery for empyema. *Ann Thorac Surg* 2005; 79: 1851–1856.
9. Andrews NCPE, Shaw RP, *et al.* Management of non-tuberculous empyema. *Am Rev Respir Dis* 1962; 85: 935–936.
10. Davies CW, Gleeson FV, Davies RJ. BTS guidelines for the management of pleural infection. *Thorax* 2003; 58: Suppl. 2, ii18–28.
11. Hughes CE, Van Scoy RE. Antibiotic therapy of pleural empyema. *Semin Respir Infect* 1991; 6: 94–102.
12. Taryle DA, Good JT Jr, Morgan EJ 3rd, *et al.* Antibiotic concentrations in human parapneumonic effusions. *J Antimicrob Chemother* 1981; 7: 171–177.
13. Vaudaux P, Waldvogel FA. Gentamicin inactivation in purulent exudates: role of cell lysis. *J Infect Dis* 1980; 142: 586–593.
14. Maskell NA, Davies CW, Nunn AJ, *et al.* U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; 352: 865–874.
15. Luh SP, Chou MC, Wang LS, *et al.* Video-assisted thoracoscopic surgery in the treatment of complicated parapneumonic effusions or empyemas: outcome of 234 patients. *Chest* 2005; 127: 1427–1432.
16. Neild JE, Eykyn SJ, Phillips I. Lung abscess and empyema. *QJM* 1985; 57: 875–882.
17. Bartlett JG. Antibiotics in lung abscess. *Semin Respir Infect* 1991; 6: 103–111.
18. Colice GL, Curtis A, Deslauriers J, *et al.* Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest* 2000; 118: 1158–1171.
19. Merriam MA, Cronan JJ, Dorfman GS, *et al.* Radiographically guided percutaneous catheter drainage of pleural fluid collections. *AJR Am J Roentgenol* 1988; 151: 1113–1116.
20. Ulmer JL, Choplin RH, Reed JC. Image-guided catheter drainage of the infected pleural space. *J Thorac Imaging* 1991; 6: 65–73.
21. Hunnam GR, Flower CD. Radiologically-guided percutaneous catheter drainage of empyemas. *Clin Radiol* 1988; 39: 121–126.
22. O'Moore PV, Mueller PR, Simeone JF, *et al.* Sonographic guidance in diagnostic and therapeutic interventions in the pleural space. *AJR Am J Roentgenol* 1987; 149: 1–5.
23. Silverman SG, Mueller PR, Saini S, *et al.* Thoracic empyema: management with image-guided catheter drainage. *Radiology* 1988; 169: 5–9.
24. Stavas J, van Sonnenberg E, Casola G, *et al.* Percutaneous drainage of infected and noninfected thoracic fluid collections. *J Thorac Imaging* 1987; 2: 80–87.
25. Crouch JD, Keagy BA, Delany DJ. "Pigtail" catheter drainage in thoracic surgery. *Am Rev Respir Dis* 1987; 136: 174–175.
26. Westcott JL. Percutaneous catheter drainage of pleural effusion and empyema. *AJR Am J Roentgenol* 1985; 144: 1189–1193.
27. Keeling AN, Leong S, Logan PM, *et al.* Empyema and effusion: outcome of image-guided small-bore catheter drainage. *Cardiovasc Intervent Radiol* 2008; 31: 135–141.
28. Rahman NM, Maskell NA, Davies CW, *et al.* The relationship between chest tube size and clinical outcome in pleural infection. *Chest* 2010; 137: 536–543.
29. Neff CC, van Sonnenberg E, Lawson DW, *et al.* CT follow-up of empyemas: pleural peels resolve after percutaneous catheter drainage. *Radiology* 1990; 176: 195–197.
30. Suchar AM, Zureikat AH, Glynn L, *et al.* Ready for the frontline: is early thoracoscopic decortication the new standard of care for advanced pneumonia with empyema? *Am Surg* 2006; 72: 688–692.

31. Anstadt MP, Guill CK, Ferguson ER, *et al.* Surgical *versus* nonsurgical treatment of empyema thoracis: an outcomes analysis. *Am J Medical Sci* 2003; 326: 9–14.
32. Bilgin M, Akcali Y, Oguzkaya F. Benefits of early aggressive management of empyema thoracis. *ANZ J Surg* 2006; 76: 120–122.
33. Tillett WS, Sherry S. The effect in patients of streptococcal fibrinolysin and streptococcal desoxyribonuclease on fibrinous, purulent, and sanguinous pleural exudations. *J Clin Invest* 1949; 28: 173–190.
34. Koegelenberg CF, Diaconi AH, Bolligeri CT. Parapneumonic pleural effusion and empyema. *Respiration* 2008; 75: 241–250.
35. Bergh NP, Ekroth R, Larsson S, *et al.* Intrapleural streptokinase in the treatment of haemothorax and empyema. *Scand J Thorac Cardiovasc Surg* 1977; 11: 265–268.
36. Berglin E, Ekroth R, Teger-Nilsson AC, *et al.* Intrapleural instillation of streptokinase. Effects on systemic fibrinolysis. *Thorac Cardiovasc Surg* 1981; 29: 124–126.
37. Fraedrich G, Hofmann D, Effenhauser P, *et al.* Instillation of fibrinolytic enzymes in the treatment of pleural empyema. *Thorac Cardiovasc Surg* 1982; 30: 36–38.
38. Davies RJ, Traill ZC, Gleeson FV. Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; 52: 416–421.
39. Bouros D, Schiza S, Tzanakis N, *et al.* Intrapleural urokinase *versus* normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, double-blind study. *Am J Respir Crit Care Med* 1999; 159: 37–42.
40. Weinstein M, Restrepo R, Chait PG, *et al.* Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. *Pediatrics* 2004; 113: e182–e185.
41. Godley PJ, Bell RC. Major hemorrhage following administration of intrapleural streptokinase. *Chest* 1984; 86: 486–487.
42. Davies CW, Lok S, Davies RJ. The systemic fibrinolytic activity of intrapleural streptokinase. *Am J Respir Crit Care Med* 1998; 157: 328–330.
43. Frye MD, Jarratt M, Sahn SA. Acute hypoxemic respiratory failure following intrapleural thrombolytic therapy for hemothorax. *Chest* 1994; 105: 1595–1596.
44. Chin NK, Lim TK. Controlled trial of intrapleural streptokinase in the treatment of pleural empyema and complicated parapneumonic effusions. *Chest* 1997; 111: 275–279.
45. Taylor RF, Rubens MB, Pearson MC, *et al.* Intrapleural streptokinase in the management of empyema. *Thorax* 1994; 49: 856–859.
46. Henke CA, Leatherman JW. Intrapleurally administered streptokinase in the treatment of acute loculated nonpurulent parapneumonic effusions. *Am Rev Respir Dis* 1992; 145: 680–684.
47. Roupie E, Bouabdallah K, Delclaux C, *et al.* Intrapleural administration of streptokinase in complicated purulent pleural effusion: a CT-guided strategy. *Intensive Care Med* 1996; 22: 1351–1353.
48. Park CS, Chung WM, Lim MK, *et al.* Transcatheter instillation of urokinase into loculated pleural effusion: analysis of treatment effect. *AJR Am J Roentgenol* 1996; 167: 649–652.
49. Bouros D, Schiza S, Tzanakis N, *et al.* Intrapleural urokinase in the treatment of complicated parapneumonic pleural effusions and empyema. *Eur Respir J* 1996; 9: 1656–1659.
50. Bouros D, Schiza S, Panagou P, *et al.* Role of streptokinase in the treatment of acute loculated parapneumonic pleural effusions and empyema. *Thorax* 1994; 49: 852–855.
51. Moulton JS, Moore PT, Mencini RA. Treatment of loculated pleural effusions with transcatheter intracavitary urokinase. *AJR Am J Roentgenol* 1989; 153: 941–945.
52. Laisaar T, Puttsepp E, Laisaar V. Early administration of intrapleural streptokinase in the treatment of multiloculated pleural effusions and pleural empyemas. *Thorac Cardiovasc Surg* 1996; 44: 252–256.
53. Jerjes-Sanchez C, Ramirez-Rivera A, Elizalde JJ, *et al.* Intrapleural fibrinolysis with streptokinase as an adjunctive treatment in hemothorax and empyema: a multicenter trial. *Chest* 1996; 109: 1514–1519.
54. Diacon AH, Theron J, Schuurmans MM, *et al.* Intrapleural streptokinase for empyema and complicated parapneumonic effusions. *Am J Respir Crit Care Med* 2004; 170: 49–53.
55. Bouros D, Schiza S, Patsourakis G, *et al.* Intrapleural streptokinase *versus* urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. *Am J Respir Crit Care Med* 1997; 155: 291–295.
56. Tuncozgur B, Ustunsoy H, Sivrikoz MC, *et al.* Intrapleural urokinase in the management of parapneumonic empyema: a randomised controlled trial. *Int J Clin Pract* 2001; 55: 658–660.
57. Cameron RJ, Davies HR. Intra-pleural fibrinolytic therapy *versus* conservative management in the treatment of adult parapneumonic effusions and empyema. *Cochrane Database Syst Rev* 2008; 2: CD002312.
58. Rahman NM, Maskell NA, West A, *et al.* Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med* 2011; 365: 518–526.
59. Landreneau RJ, Keenan RJ, Hazelrigg SR, *et al.* Thoracoscopy for empyema and hemothorax. *Chest* 1996; 109: 18–24.
60. Chambers A, Routledge T, Dunning J, *et al.* Is video-assisted thoracoscopic surgical decortication superior to open surgery in the management of adults with primary empyema? *Interact Cardiovasc Thorac Surg* 2010; 11: 171–177.

61. Tong BC, Hanna J, Toloza EM, *et al.* Outcomes of video-assisted thoracoscopic decortication. *Ann Thorac Surg* 2010; 89: 220–225.
62. Chan DT, Sihoe AD, Chan S, *et al.* Surgical treatment for empyema thoracis: is video-assisted thoracic surgery "better" than thoracotomy? *Ann Thorac Surg* 2007; 84: 225–231.
63. Cardillo G, Carleo F, Carbone L, *et al.* Chronic postpneumonic pleural empyema: comparative merits of thoracoscopic *versus* open decortication. *Eur J Cardiothorac Surg* 2009; 36: 914–918.
64. Solaini L, Prusciano F, Bagioni P. Video-assisted thoracic surgery in the treatment of pleural empyema. *Surg Endosc* 2007; 21: 280–284.
65. Molnar TF. Current surgical treatment of thoracic empyema in adults. *Eur J Cardiothorac Surg* 2007; 32: 422–430.
66. Striffeler H, Gugger M, Im Hof V, *et al.* Video-assisted thoracoscopic surgery for fibrinopurulent pleural empyema in 67 patients. *Ann Thorac Surg* 1998; 65: 319–323.
67. Wait MA, Sharma S, Hohn J, *et al.* A randomized trial of empyema therapy. *Chest* 1997; 111: 1548–1551.
68. Waller DA, Rengarajan A. Thoracoscopic decortication: a role for video-assisted surgery in chronic postpneumonic pleural empyema. *Ann Thorac Surg* 2001; 71: 1813–1816.
69. Waller DA, Rengarajan A, Nicholson FH, *et al.* Delayed referral reduces the success of video-assisted thoracoscopic debridement for post-pneumonic empyema. *Respir Med* 2001; 95: 836–840.
70. Roberts JR. Minimally invasive surgery in the treatment of empyema: intraoperative decision making. *Ann Thorac Surg* 2003; 76: 225–230.
71. Angelillo-Mackinlay T, Lyons GA, Piedras MB, *et al.* Surgical treatment of postpneumonic empyema. *World J Surg* 1999; 23: 1110–1113.
72. Cassina PC, Hauser M, Hillejan L, *et al.* Video-assisted thoracoscopy in the treatment of pleural empyema: stage-based management and outcome. *J Thorac Cardiovasc Surg* 1999; 117: 234–238.
73. Rzyman W, Skokowski J, Romanowicz G, *et al.* Decortication in chronic pleural empyema – effect on lung function. *Eur J Cardiothorac Surg* 2002; 21: 502–507.
74. Swoboda L, Laule K, Blattmann H, *et al.* Decortication in chronic pleural empyema. Investigation of lung function based on perfusion scintigraphy. *Thorac Cardiovasc Surg* 1990; 38: 359–361.
75. Deslauriers J, Jacques LF, Gregoire J. Role of Eloesser flap and thoracoplasty in the third millennium. *Chest Surg Clin N Am* 2002; 12: 605–623.
76. Fournier I, Krueger T, Wang Y, *et al.* Tailored thoracomyoplasty as a valid treatment option for chronic postlobectomy empyema. *Ann Thorac Surg* 2012; 94: 387–393.
77. Botianu PV, Dobrica AC, Butiurca A, *et al.* Complex space-filling procedures for intrathoracic infections – personal experience with 76 consecutive cases. *Eur J Cardiothorac Surg* 2010; 37: 478–481.
78. Krassas A, Grima R, Bagan P, *et al.* Current indications and results for thoracoplasty and intrathoracic muscle transposition. *Eur J Cardiothorac Surg* 2010; 37: 1215–1220.
79. Stefani A, Jouni R, Alifano M, *et al.* Thoracoplasty in the current practice of thoracic surgery: a single-institution 10-year experience. *Ann Thorac Surg* 2011; 91: 263–268.
80. Garcia-Yuste M, Ramos G, Duque JL, *et al.* Open-window thoracostomy and thoracomyoplasty to manage chronic pleural empyema. *Ann Thorac Surg* 1998; 65: 818–822.
81. Saadi A, Perentes JY, Gonzalez M, *et al.* Vacuum-assisted closure device: a useful tool in the management of severe intrathoracic infections. *Ann Thorac Surg* 2011; 91: 1582–1589.

Chapter 13

Pleural empyema in children

Jeroen M.H. Hendriks, Martine Sabbe#, Jan Verhaegen¶, Patrick Lauwers*, Stijn Verhulst+ and Paul E.Y. Van Schil**

SUMMARY: Parapneumonic effusion and pleural empyema in children are more frequently encountered in the age group >2 years. This is explained by routine vaccination with the pneumococcal conjugated vaccine for *Streptococcus pneumoniae* in children aged <2 years. In every child treated for a lower respiratory tract infection, a complicated pneumonia should be suspected in case of clinical changes. Differential diagnosis and treatment are based on radiographic assessment with ultrasonography and computed tomographic scan of the chest, and biochemical and microbiological analysis of the pleural fluid. For early cases of parapneumonic effusion, drainage with a small drain (⩽16 French) is advised. In the case of loculation or a pleural peel, thoracoscopic surgery is indicated. For more severe cases, a thoracotomy or a conservative treatment with surgery in a second stage is advised, especially for lung abscesses. Intrapleural fibrinolysis has shown contradictory results, but a recent prospective trial showed great promise for the combination of fibrinolysis and DNAse for stage 1 and 2 complicated pneumonia.

*Dept of Thoracic and Vascular Surgery, and
+Dept of Paediatrics, Antwerp University Hospital, Edegem,
#Public Health and Surveillance, Scientific Institute of Public Health, Brussels, and
¶National Reference Centre for Pneumococci, University Hospitals Leuven, Leuven, Belgium.

Correspondence: J.M.H. Hendriks, Dept of Thoracic and Vascular Surgery, Antwerp University Hospital, Wilrijkstraat 10, B-2650 Edegem, Belgium.
Email: Jeroen.hendriks@uza.be

Eur Respir Monogr 2013; 61: 153–161.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041612
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Each year, up to 2.6 million cases of pneumonia are diagnosed in developed countries in children aged <5 years [1]. *Streprococcus pneumoniae* is still the leading cause of bacterial pneumonia [2] and empyema, accounting for >50% of the cases [3]. Since 2006, the incidence of invasive pneumococcal infections serotypes included in the seven-valent pneumococcal conjugated vaccine (PCV7) has decreased in Belgium for children ⩽2 years of age due to the introduction of a pneumococcal conjugated vaccine by the government. However, the incidence of empyema is increasing, especially in the 2–4-year-old age group, in part by the emergence of pneumococcal serotypes not covered in the PCV7 (serotypes 1, 3 and 19A) and by *Staphylococcus aureus*. A further decrease is expected since the introduction of the 13-valent pneumococcal conjugated vaccine (PCV13) in September 2011. One-third of the reported cases of pneumococcal pneumonia were complicated by parapneumonic effusion (PPE), empyema and abscess formation [4, 5].

During the last decade, treatment techniques of PPE and empyema have not changed dramatically, but a remarkable shift towards less invasive techniques, such as thoracoscopic treatment, has been noticed. These less invasive techniques can be implemented more quickly in the early course of a PPE, probably to avoid evolution to a frank empyema.

The development of PPE and empyema has not been studied in a systematic way, but rapid progression from an uncomplicated infection into an organised empyema is well known to everyone who has dealt with such cases in children. Therefore, it is essential to pay special attention to every child being treated for a lower airway infection to detect a PPE or empyema as early as possible, as the ease of treatment is directly related to its stage.

Whereas most physicians agree that the initial exudative stage or simple PPE usually can be treated either by a wait-and-see attitude or a chest tube, much debate is ongoing regarding the subsequent fibrinopurulent stage, which often requires more invasive treatment. For the last stage, organised empyema, the discussion is more focused on an endoscopic *versus* open surgical treatment, and the optimal moment to install such a therapy, especially in the case of an underlying pulmonary problem.

Therefore, it is important not only to detect a complicated pneumonia, but also to install the correct treatment as early as possible and in a stepwise way. In order to do so, knowledge of the stages and differentiation between the stages is essential. Gaining experience in all these aspects of diagnosis and treatment is essential if these children are to be treated in a fast and proper manner to avoid any delay in correct treatment or an increased complication rate. Multidisciplinary teams of paediatricians, surgeons and radiologists are of utmost importance in these cases.

Incidence and prevention

Available estimates suggest that each year, in the developed countries, up to 2.6 million cases of pneumonia are diagnosed in children aged <5 years, of which one-half is hospitalised. Of these, around 3000 will die [1]. The leading cause of bacterial pneumonia and empyema in children is *S. pneumoniae* [2]. Since 2006, clinical data and vaccination status regarding *S. pneumoniae* are collected in Belgium by a surveillance network of paediatricians called "Pedisurv", which is linked to the National Reference Laboratory (NRL) of *S. pneumoniae* [4, 5]. The NRL receives isolates from a stable number of ~100 hospital laboratories distributed all over the country. *S. pneumoniae* is also included in this surveillance network. In 2004, PCV7 was introduced in Belgium; it became free of charge in January 2007. In October 2010, the Superior Health Council of Belgium recommended the substitution of PCV7 by PCV13, which has been implemented since September 2011 in all children aged <2 years. In 2012, PCV13 uptake was estimated to be 89–97%. The vaccine strategy is a 2+1 dose schedule (two doses at 2 and 4 months, and one booster dose at 12–13 months). A catch-up strategy is provided until 24 months of age. Between 2006 and 2011, 2534 cases of invasive pneumococcal disease (IPD) were observed in children aged ⩽15 years. An IPD is defined as the isolation of *S. pneumoniae* from a normally sterile bodily fluid, such as blood, pleural fluid or cerebrospinal fluid In 2011, 481 cases of invasive pneumococcal infection were seen, the highest number since 2006. Compared with 2006 and the period 2002–2003, the incidence decreased for children aged <2 years, but for children aged 2–4 years, the rate increased in 2011 compared with 2006. Rates attributable to PCV7 decreased significantly in all age groups, but non-PCV7 serotype rates increased. These non-PCV7 serotypes seem to be particularly responsible for the increase in empyema complicating pneumococcal pneumonia [3]. The effect of routine vaccination with the PCV13 is expected to be seen in 2012. In answer to the constant resistance of new serotypes to the current vaccines, several protein vaccines for pneumococcal infections are developed with the aim to induce a noncapsular polysaccharide specific immune response. Of all IPD cases since 2006, 1069 cases were classified as pneumococcal pneumonia, of which 67% were uncomplicated. Of the 33% complicated cases, pleural effusion was present in 20%, empyema in 12% and abscess formation in 1%. In 73 cases of pneumococcal empyema, a serotype was identified; 41% belonged to serotype 1, 25% had serotype 5, 19% serotype 19A and 5% had serotype 7F (table 1) [4, 5].

Diagnosis and classification

Suspicion of a PPE or empyema increases whenever a child presents with persistent fever or increased oxygen requirement despite patient-triggered antibiotics. The shift from an upper airway

Table 1. Incidence of pneumococcal pneumonia among children per 100 000 population, by age group, each year in Belgium [4]

	2006	2007	2008	2009	2010	2011
Age <2 years						
Pneumococcal pneumonia all	23.54	26.69	14.99	28.03	33.41	21.92
Uncomplicated	14.23	22.42	11.66	19.24	28.35	17.74
Complicated	9.31	4.27	3.33	8.79	5.06	4.17
With empyema	2.19	0.53	2.22	3.85	1.52	1.57
With pleural effusion	7.12	2.67	1.11	4.95	3.54	2.61
With abscess	0.00	1.07	0.00	0.00	0.00	0.00
Age 2–4 years						
Pneumococcal pneumonia all	20.96	22.93	22.05	33.57	26.92	47.33
Uncomplicated	11.97	17.38	15.21	19.62	20.02	27.05
Complicated	8.98	5.55	6.84	13.96	6.90	20.28
With empyema	3.74	2.22	1.52	5.66	3.45	8.54
With pleural effusion	5.24	3.33	4.56	7.54	3.45	10.68
With abscess	0.00	0.00	0.76	0.75	0.00	1.07
Age 5–15 years						
Pneumococcal pneumonia all	4.40	5.08	3.19	6.96	5.30	4.80
Uncomplicated	3.17	3.46	2.24	3.83	3.57	3.24
Complicated	1.23	1.63	0.94	3.13	1.73	1.57
With empyema	0.31	0.30	0.24	0.93	0.65	0.31
With pleural effusion	0.92	1.32	0.71	1.97	1.08	1.25
With abscess	0.00	0.00	0.00	0.23	0.00	0.00

infection into one with a PPE can occur in hours, as seen in figure 1. The diagnosis of a PPE is made by diminished breath sounds, increased need for oxygen and the presence of fluid on a chest radiograph and/or ultrasonography of the thorax. During the first exudative phase, the pleura swells and large amounts of exudate are produced that accumulate within the pleural space. In the second fibrinopurulent phase, heavy fibrin deposits are formed that cover the pleura; the pleural fluid becomes turbid and thickened. In the last organisational phase, which takes place ~2 weeks after the onset, fibroblasts grow in and collagen fibres are formed to create a thick peel on the lung surface resulting in an entrapment of the lung. Once pleural fluid is detected, the amount of fluid and laboratory assessment of the fluid can help to classify a patient. One has to remember that these classifications make suggestions regarding treatment that can be of help with direct treatment, but evidence, especially regarding the use of thrombolytics, to support them is either poor or absent. Four important classifications have been published over the years [6–9], but we prefer to use the classification by the British Thoracic Society (table 2).

Evaluation and imaging

Once a child is admitted to the hospital and the diagnosis of a PPE is made on chest radiograph, a dedicated team of at least one radiologist, one paediatrician and one surgeon (thoracic or paediatric) has to decide what treatment, besides intravenous antibiotics, is necessary for immediate relief from this fluid and to further restrict development towards the fibrinopurulent and/or organisational stages, if these are not already present. The length of antibiotic therapy in children for a PPE or empyema is at least 10 days after resolution of fever [10].

Data from adults suggest that effusions larger than 40–50% require drainage, but this is unproven in the paediatric population. A retrospective study suggests that a rim of fluid of <2 cm or pleural fluid that opacifies less than one-half of the thorax does not need drainage [11]. When children are symptomatic, which is the case in most children referred to a specialised hospital, the amount of fluid is of less importance and drainage is always advised. This drainage is performed by ultrasound-guided needle aspiration or by insertion of a chest drain. A chest drain is placed when aspiration fails to solve the problem or when frank pus is evacuated (fig. 2). The fluid or pus is always examined for pH and bacterial load. We routinely measure pH immediately in a blood gas

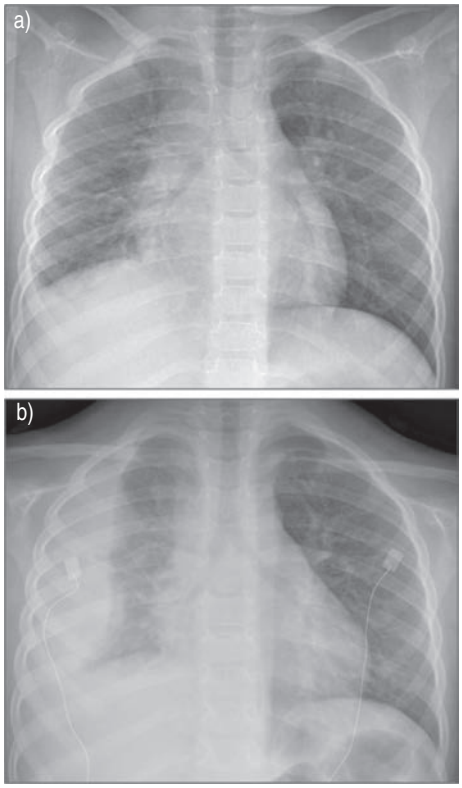


Figure 1. Evolution of a parapneumonic effusion in a 4-year-old female under antibiotic treatment for an upper airway infection. Chest radiograph a) on day 20, and b) 48 h later.

analyser that is present in the operating complex. Addition of heparin in the syringe used to take the sample for pH analysis is not advised, as it is well known this may alter the pH value. An empyema is diagnosed as soon as the pleural fluid contains pus, which is characterised by a viscous whitish-yellow, turbid-to-opaque fluid (fig. 3c). This fluid consists of fibrin, cellular debris and viable or dead bacteria. The presence of pathogens in a nonpurulent pleural fluid or the results of chemical pleural fluid analysis (low pH) do not define an empyema. The latter is defined as an undetermined or complicated PPE. A low pH (pH<7.2), however, is an indicator for a poor outcome, and drainage or further treatment is essential in this case. After pH analysis, the fluid is sent to the laboratory for further analysis, but this should not delay appropriate treatment. A computed tomography (CT) scan in addition to a chest radiograph is often advised, especially when an advanced stage of PPE (pleural thickening or loculations) is expected or to rule out an underlying parenchymal problem (abscesses and bronchopleural fistulae). In these cases, low-dose CT and protection of radiosensitive organs, such as the thyroid, testicles or ovaries, are essential. For the detection of fibrin strands or septations within the pleural fluid (pre-stage of loculations), CT is inferior to ultrasound (fig. 4) [12].

Drainage

As already mentioned, when children are symptomatic, which is the case in most children referred to a specialised hospital, the amount of fluid is of less importance and drainage is always advised. When drainage is preferred, a chest drain is placed either under sedation (in older child aged >16 years) or under general anaesthesia (children aged <16 years or if preferred when aged >16 years), but always in the operating theatre and with good pre-operative preparation. Fluoroscopic or ultrasound guidance during placement of the drain can help to guide the drain immediately into the correct position. In case the fluid is not drained sufficiently on fluoroscopy, a pleuroscopy or thoracoscopy can be performed at once in order to visualise the pleura, to define the stage of PPE and to install endosurgical treatment. This, of course, is discussed in advance with the parents as part of the treatment. No difference between a chest tube larger or smaller than 14 French has been observed regarding the outcome of drainage in adults [13]; also, no difference has been noted between a chest tube and a pigtail catheter [14].

Table 2. Classification of a parapneumonic effusion (PPE) or empyema as proposed by the British Thoracic Society [9]

	Uncomplicated or simple PPE	Complicated PPE	Empyema
Fluid appearance	Clear/thin	Clear or cloudy/turbid	Frank pus
pH	>7.20	<7.20	<7.20
Bacteria	Sterile	Present/not present	Present
Lactate dehydrogenase	<1000 IU·L^{-1}	>1000 IU·L^{-1}	>1000 IU·L^{-1}
Glucose	>2.2 mmol·L^{-1}	>2.2 mmol·L^{-1}	<40 mg·dL^{-1}; <2.2 mmol·L^{-1}

In our hospital, we prefer a small-sized chest tube, such as size 16 French, in children aged >5 years, and a smaller one in younger children. Additional holes on the radiopaque line of the drain made by the surgeon can help to drain the pleural cavity from the top to the bottom with less risk of obstruction of the drain by the fluid.

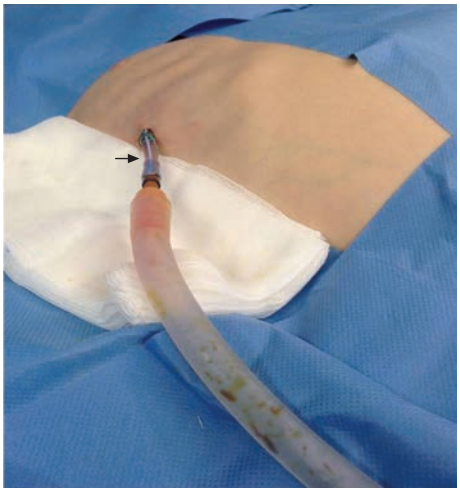


Figure 2. A 16 French chest tube drain (arrow) is placed under fluoroscopic guidance on the operating table under general anaesthesia for a parapneumonic effusion.

Thoracoscopy

In the case of empyema, multiple loculations, a thickened visceral pleura or insufficient drainage of the pleural fluid by a chest tube, a larger chest tube is useless and an immediate thoracoscopic evaluation of the pleural space is essential (fig. 5). A video-assisted thoracoscopic surgery (VATS) procedure results in earlier and more complete resolution of empyema compared with chest tube alone [15–17]. A thoracoscopic procedure is performed under general anaesthesic with the patient in a lateral decubitus position. In trained hands and with paediatric instruments, a VATS debridement of a stage 2 or even peeling of a thickened visceral peel is technically possible and, therefore, preferred over open surgery. A good suction device is essential for these procedures and is delivered through a 5-mm port. Insufflation of carbon dioxide under low pressure (<7 mmHg) can help to create space to work within the pleural cavity.

Fibrinolysis

The place of fibrinolysis in empyema is unclear. A number of small randomised placebo-controlled trials evaluating intrapleural streptokinase and urokinase in pleural infection have

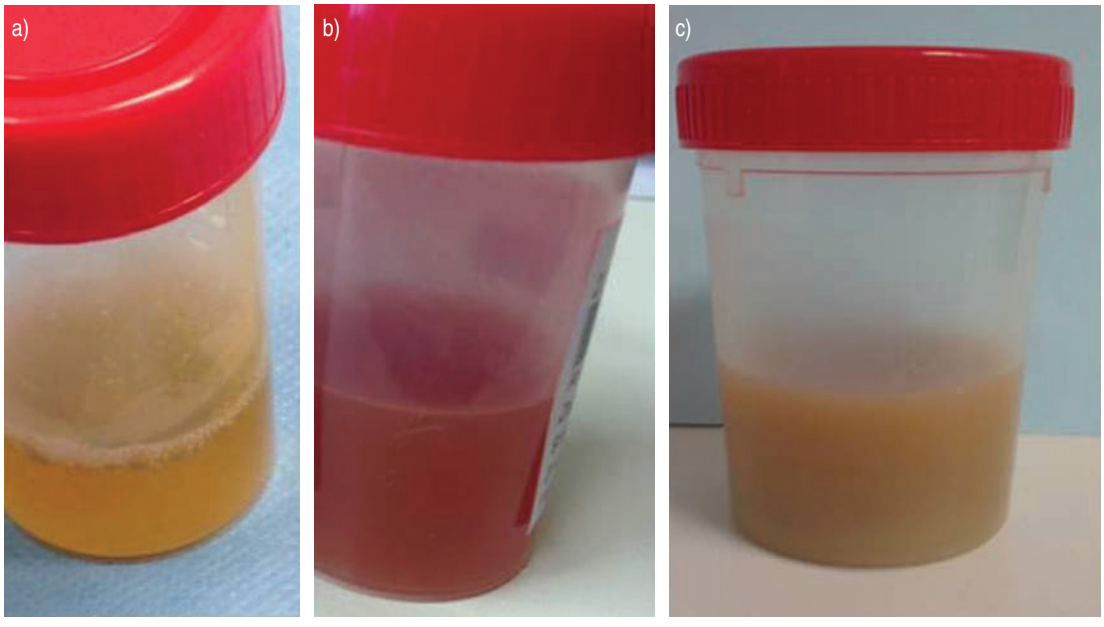


Figure 3. Pleural fluid appearance from stage 1 to stage 3. a) Clear fluid, b) cloudy or turbid fluid and c) frank pus.

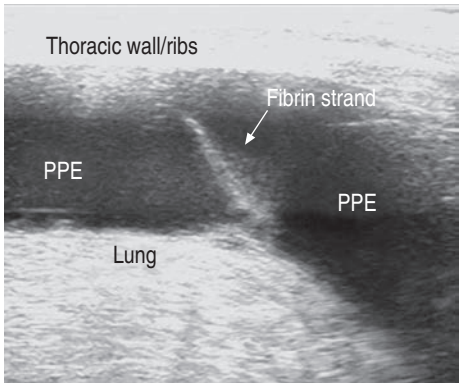


Figure 4. Ultrasound of the thorax clearly shows the amount of fluid and presence of fibrin strands. PPE: parapneumonic effusion.

suggested a potential benefit from the intervention in all [18–21] but one case [22]. In addition, the 2008 Cochrane review included subgroup analysis and came to the conclusion that an overall benefit to the use of fibrinolytics is present in the group with loculations [23]. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee 2011–2012 [24] concluded that it is reasonable to utilise chemical debridement with a fibrinolytic agent (tissue plasminogen activator (tPA) in the USA) for 3 days before deciding to proceed with a thoracoscopic procedure. This grade B recommendation was based on the results from positive trials and the fact that children are involved. In contrast, the Multicenter Intrapleural Sepsis Trial (MIST)1 study [22], a Cochrane review [25] and a meta-analysis of a placebo-controlled trial of intrapleural fibrinolytic therapy in pleural infection [26] failed to show sufficient direct evidence of clinical utility of intrapleural fibrinolytic therapy as a routine use in pleural infection to alter outcome parameters, such as the need for surgery, death or hospital stay. This is supported by laboratory findings that a fibrinolytic agent alone is no different to saline in changing the pus viscosity [27, 28]. The success of fibrinolytic therapy is based entirely on the initial positive results reported by TILLETT and SHERRY [29] in 1949. However, they used both streptokinase and

Figure 5. Parapneumonic effusion stage 2, for which video-assisted thoracic surgery debridement was used. a) Computed tomography scan of the chest, b) thoracoscopic view within the chest showing many fibrin strands after evacuation of the pleural fluid, c) end result after debridement, and d) fibrin and debris removed from the chest cavity.

Table 3. Video-assisted thoracoscopic surgery *versus* fibrinolysis in children: prospective, randomised trials

	Wait [31]	Sonnappa [32]	St Peter [33]	Cobanoglu [34]
Country and year of study	USA 1997	UK 2006	USA 2009	Turkey 2011
Arms	Streptokinase VATS	Urokinase VATS	tPA VATS	Streptokinase VATS
Patients n	2×10	2×30	2×18	2×27
Mortality %				0
Overall success rate				No difference
Hospital days after intervention	Lower for VATS; $p<0.01$	No difference	No difference	Lower for VATS; $p<0.01$
Chest tube duration	Lower for VATS; $p<0.05$			Lower for VATS; $p<0.01$
Cost	No difference	In favour of urokinase	In favour of tPA	In favour of streptokinase

tPA: tissue plasminogen activator; VATS: video-assisted thoracoscopic surgery.

streptodornase, a DNase enzyme produced by streptococcal bacteria [29]. This finding is supported by the recently published UK MIST2 trial [30]. In this trial, four different intrapleural therapies were given through a chest tube: placebo, tPA, DNAse or tPA+DNAse. Main outcome parameters were resolution of the effusion on chest radiograph and a reduced number of hospital days. No difference was seen for the tPA and DNAse groups compared with placebo. However, the combination of tPA+DNAse was significantly better compared with all the other groups. As reported by the principal investigator of the MIST2 trial, important end-points, such as the proportion of patients referred for thoracic surgery, are not yet proven, and the trial was only performed in 52 patients, which is a low number to define this as a safe treatment. These remarks indicate that further trials are needed.

Regarding surgery, four prospective trials in three different countries have been performed comparing VATS with fibrinolysis in children [31–34]. However, these trials used different fibrinolytic agents and different regimens complicating inter-trial comparison. In two of these four studies, no difference was seen between fibrinolysis and VATS regarding length of treatment or outcome, but costs were higher for the VATS arm. For two other studies, a clear difference was seen in favour of VATS. Details of these studies are depicted in table 3. In another prospective randomised trial by Kurt *et al.* [35], VATS was compared with tube chest drainage, but both groups received fibrinolysis with reteplase in case of persistent effusion. A small group of 18 patients was randomised into two groups. Hospital length of stay, number of chest tube days, narcotic use, number of radiographic procedures and additional interventional procedures were all fewer for the VATS group. In addition, none of the patients within the VATS group needed additional fibrinolytic therapy [35].

Thoracotomy

Approach by thoracotomy is performed either when thoracoscopic treatment fails or whenever resection of lung tissue is necessary. Failure of thoracoscopic treatment is caused by poor visualisation of the pleural cavity, uncontrolled bleeding, a pleural peel that cannot be removed or recurrence of infection despite initial good results of thoracoscopic debridement. Resection of lung tissue is usually preserved for a lung abscess or necrotising pneumonia. These latter complications of a pneumonia are usually detected by CT scan on admittance of the child or during hospitalisation for recurrent disease after initial drainage or thoracoscopic therapy. The general opinion, despite the lack of studies, is to postpone surgery for as long as possible. When the abscess is located in the periphery of the lung without contact with the airway, a CT- or

ultrasound-guided drainage in combination with intravenous antibiotics can usually solve the problem and helps to shorten the hospital stay [36]. In the case of necrosis, a thoracotomy is usually indicated, but the risks of air leakage and bronchopleural fistula are high. Resection can be necessary at an earlier stage when the abscess is located more centrally and in close proximity to the large vessels, especially in immunocompromised children with the diagnosis of aspergillus, to prevent fatal haemorrhage.

Conclusions

PPE and pleural empyema in children are important complications of pneumonia and their incidence is increasing. Regarding *S. pneumoniae*, a shift towards older children has been observed, as children aged <2 years are routinely vaccinated against this infection. A high index of suspicion of a complicated pneumonia is necessary in every child treated with antibiotics for an upper airway infection, especially when the child is not recovering or when new symptoms arise. Diagnosis is made by puncture of the fluid, ultrasound examination and a low-dose CT scan of the chest. Once the diagnosis of a PPE or empyema is made, either drainage or a thoracoscopic procedure is performed. For a PPE, drainage *via* a chest tube is usually sufficient. In the case of empyema, the addition of fibrinolytic agents before proceding to thoracoscopic surgery is advised, but studies and conclusions regarding these studies are conflicting. A recent trial investigating the combination of a fibrinolytic agent and DNAse has shown promising results, but further studies are needed to define the advantages in other end-points and to demonstrate its safety in larger groups of patients. In the case of an abscess or necrosis, a conservative strategy is recommended, with surgery as a second stage. Open surgery in the first stage is only performed in the case of failed thoracoscopic surgery or when a lung abcess has ruptured into the pleural cavity.

Statement of Interest
None declared.

References

1. Madhi SA, De Wals P, Grijalva CG, *et al.* The burden of childhood pneumonia in the developed world: a review of the literature. *Pediatr Infect Dis J* 2013; 32: e119–e127.
2. O'Brien KL, Wolfson LJ, Watt JP, *et al.* Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; 374: 893–902.
3. Burgos J, Falco V, Pahissa A. The increasing incidence of empyema. *Curr Opin Pulm Med* 2013; 19: 350–356.
4. Hanquet G, Lernout T, Vergison A, *et al.* Impact of conjugate 7-valent vaccination in Blegium: addressing methodological challenges. *Vaccine* 2011; 29: 2856–2864.
5. Kissling E. Sensitivities of invasive pneumococcal disease surveillance systems in Belgium, October 2005 to September 2006: capture–recapture study in children. Brussels, ISP/WIV, 2008. Report number 2008–036.
6. Bouros D. Parapneumonic pleural effusions and empyema. *In:* Bouros D, ed. Pleural Disease. New York, Informa, 2009; pp 308–338.
7. Light RW. A new classification of parapneumonic effusions and empyema. *Chest* 1995; 108: 299–301.
8. Colice GL, Curtis A, Deslauriers J, *et al.* Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest* 2000; 118: 1158–1171.
9. Davies CW, Gleeson FV, Davies RJ. BTS guidelines for the management of pleural infection. *Thorax* 2003; 58: Suppl. 2, ii18–ii28.
10. Bradley JS, Byington CL, Shah SS, *et al.* Executive summary: the management of community acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Disease Society and the Infectious Disease Society of America. *Clin Infect Dis* 2011; 53: 617–630.
11. Carter E, Waldhausen J, Zhang W, *et al.* Management of children with empyema: pleural drainage is not always necessary. *Pediatr Pulmonol* 2010; 45: 475–480.
12. Calder A, Owens CM. Imaging of parapneumonic pleural effusions and empyema in children. *Pediatr Radiol* 2009; 39: 527–537.
13. Rahman NM, Maskell NA, Davies CW, *et al.* The relationship between chest tube size and clinical outcome in pleural infection. *Chest* 2010; 137: 536–543.
14. Lin CH, Lin WC, Chang JS. Comparison of pigtail catheter with chest tube for drainage of parapneumonic effusion in children. *Pediatr Neonatol* 2011; 52: 337–341.

15. Gates R, Hogan M, Weinstein S, *et al.* Drainage, fibrinolytics, or surgery: a comparison of treatment options in pediatric empyema. *J Pediatr Surg* 2004; 39: 1638–1642.
16. Kurt B, Winterhalter K, Connors R, *et al.* Therapy of parapneumonic effusions in children: video-assisted thoracoscopic surgery *versus* conventional thoracostomy drainage. *Pediatrics* 2006; 118: 547–553.
17. Aziz A, Healy J, Qureshi F, *et al.* Comparative analysis of chest tube thoracostomy and video-assisted thoracoscopic surgery in empyema and parapneumonic effusion associated with pneumonia in children. *Surg Infect* 2008; 9: 317–323.
18. Bouros D, Schiza S, Tzanakis N, *et al.* Intrapleural urokinase *versus* normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, double-blind study. *Am J Respir Crit Care Med* 1999; 159: 37–42.
19. Singh M, Mathew JL, Chandra S, *et al.* Randomized controlled trial of intrapleural streptokinase in empyema thoracis in children. *Acta Paediatr* 2004; 93: 1443–1445.
20. Tuncozgur B, Ustunsoy H, Sivrikoz M, *et al.* Intrapleural urokinase in the management of parapneumonic empyema: a randomized controlled trial. *Int J Clin Pract* 2001; 55: 658–660.
21. Diacon AH, Theron J, Schuurmans MM, *et al.* Intrapleural streptokinase for empyema and complicated parapneumonic effusions. *Am J Respir Crit Care Med* 2004; 170: 49–53.
22. Maskell NA, Davies W, Nunn AJ, *et al.* UK controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; 352: 865–874.
23. Cameron R, Davies HR. Intrapleural fibrinolytic therapy *versus* conservative management in the treatment of adult parapneumonic effusions and empyema. *Cochrane Database Syst Rev* 2008: CD002312.
24. Islam S, Calkins CM, Goldin AB, *et al.* The diagnosis and management of empyema in children: a comprehensive review from the APSA Outcomes and Clinical Trials Committee. *J Pediatr Surg* 2012; 47: 2101–2110.
25. Cameron R, Davies HR. Intra-pleural fibrinolytic therapy *versus* conservative management in the treatment of parapneumonic effusions and empyema. *Cochrane Database Syst Rev* 2004: CD002312.
26. Tokuda Y, Matsushima D, Stein GH, *et al.* Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. *Chest* 2006; 129: 783–790.
27. Simpson G, Roomes D, Heron M. Effects of streptokinase and deoxyribonuclease on viscosity of human surgical and empyema pus. *Chest* 2000; 117: 1728–1733.
28. Light RW, Nguyen T, Mulligan ME, *et al.* The *in vitro* efficacy of varidase *versus* streptokinase or urokinase for liquefying thick purulent exudative material from loculated empyema. *Lung* 2000; 178: 13–18.
29. Tillett WS, Sherry S. The effect in patients of streptococcal fibrinolysin (streptokinase) and streptococcal deoxyribonuclease on fibrinous, purulent and sanguinous pleural exsudations. *J Clin Invest* 1949; 28: 173–190.
30. Rahman NM, Maskell NA, West A, *et al.* Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med* 2011; 365: 518–526.
31. Wait MA, Sharma S, Hohn J, *et al.* A randomized trial of empyema therapy. *Chest* 1997; 111: 1548–1551.
32. Sonnappa S, Cohen G, Owens CM, *et al.* Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema. *Am J Respir Crit Care Med* 2006; 174: 221–227.
33. St Peter SD, Tsao K, Harrison C et al. Thoracoscopic decortication *versus* tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. *J Pediatr Surg* 2009; 44: 106–111.
34. Cobanoglu U, Sayir F, Bilici S, *et al.* Comparison of the methods of fibrinolysis by tube thoracotomy and thoracoscopic decortication in children with stage II and III empyema: a prospective randomized trial. *Pediatr Rep* 2011; 3: e29.
35. Kurt B, Winterhalter K, Connors R, *et al.* Therapy of parapneumonic effusions in children: video-assisted thoracoscopic surgery *versus* conventional thoracostomy drainage. *Pediatrics* 2006; 118: 547–553.
36. Patradoon-Ho P, Fitzgerald DA. Lung abscess in children. *Paediatr Respir Rev* 2007; 8: 77–84.

Chapter 14

Lung resection in the presence of infection and after pleural empyema

Dragan Subotic[*] *and Francoise Le Pimpec Barthes*[#]

SUMMARY: There are two forms of infection that may precede a lung resection: 1) lung infection without previous pleural empyema; and 2) pleural empyema preceding a lung resection. The first form refers mainly to the operation of cavitating tumours with or without clinical signs of infection. Although some studies detailing protected brush and lung tissue biopsies confirmed colonisation with one or more potential pathogens in 41% patients, no major practical benefit from performing biopsies was observed, as the post-operative infection rate was low (12%) and without correlation with bronchial colonisation. Current imaging techniques are unreliable in differentiating in situ infection from necrosis in cavitating lung tumours. Furthermore, a severe and putrid infection within a tumour may be not clinically evident before surgery. The association between empyema and malignant disease reached 22% in 1994, with 80% of malignancies representing a lung cancer. Mortality for empyema associated with malignant disease is 60–80%. In these patients, surgery is possible only after full control of infection and pleural space obliteration is achieved.

[*]Clinic for Thoracic Surgery, Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia.
[#]Service de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, Paris, France.

Correspondence: D. Subotic, Clinic for Thoracic Surgery, Clinical Center of Serbia, University of Belgrade School of Medicine, Belgrade, Serbia.
Email: profsubotic@gmail.com

Eur Respir Monogr 2013; 61: 162–170.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041812
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

There are two clinical forms of infection that may precede a lung resection: 1) lung infection without previous pleural empyema; and 2) pleural empyema preceding a lung resection. In the first situation, contamination of the operative field may ensue due to the rupture of a necrotic tumour during the operation or due to spillage of endobronchial secretions at the moment of dividing the bronchus. The second situation refers to pleural empyema, either recognised and treated or unrecognised before the operation, thus leading to intra-operative contamination.

Although these two forms of infection may exist both in patients with malignant and nonmalignant pathology, they represent a more difficult problem in patients with malignant disease when considering the oncological aspect that is to be dealt with simultaneously with the problem of infection. For this reason, the present chapter refers mostly to infectious problems associated with lung cancer surgery.

Lung resection in the presence of intrapulmonary infection

Controlled studies specifically addressing the correlation between pre-operative bacterial infection and post-operative complications are rare. In the prospective study of 194 patients without pre-operative clinical signs of infection by SOK *et al.* [1], it was demonstrated that, in patients with post-operative infection, potential pathogens were isolated from pre-operative sputum samples in 18%, from intra-operative bronchial brushes in 13% and from post-operative sputum samples in as much as in 63% of operated patients. Although it could be concluded that pathogens responsible for post-operative infectious complications may be acquired post-operatively from the oral cavity, pharynx and hypopharynx of the patient, such a conclusion should be accepted with caution, as a high proportion of patients in both the study by SOK *et al.* [1] and other reported studies received antibiotic prophylaxis post-operatively for at least several days as standard procedure.

Literature data are quite contradictory. In a study by IOANAS *et al.* [2] of 41 patients operated on for lung cancer, intra-operative samples were collected by performing protected brush and lung tissue biopsies. Although, in 41% of patients, colonisation with one or more potential pathogens existed, the post-operative infection rate was low (12%) and without correlation with bronchial colonisation.

Thus, in the absence of clear literature recommendations, the registering of eventual signs of infection and empirical administration of antibiotics according to accepted principles is still a frequent practice.

In order to overcome this problem, in some prospective studies with a high incidence of post-operative pneumonia (POP), in which early POP was often related to colonising bacteria, a change of the antibiotic prophylaxis regimen was attempted. Regimen change was attempted because of frequent resistance to second generation cephalosporin employed for antibiotic prophylaxis in that study [3]. With the new regime (a short-term (24-h), high-dose (6-g) course of amoxicillin-clavulanate), a significant decrease in POP and in the overall need for post-operative antibiotics was observed [4]. However, the proportion of bacterial documentation among cases of POP, the occurrence of bronchitis and empyema, and the need for antibiotic therapy for nonrespiratory causes did not change.

A large clinical series, studied by YAMADA *et al.* [5], of 626 patients with lung cancer treated by surgery was expected to elucidate this problem. In that study [5], POP occurred in 6.4% of patients, with significant differences among chronic obstructive pulmonary disease (COPD) (14.3%) and non-COPD patients (3.6%). Pre-operative colonisation by potentially pathogenic micro-organisms existed in 12.8% of patients. Unfortunately, again no correlation between the bacteria responsible for pre-operative colonisation and subsequent POP was found. The author's suggestion [5], supported by SETHI *et al.* [6], that, in COPD patients, POP resulted more frequently from infection with new pathogens rather than from infection by bacteria responsible for colonisation, was of no major practical benefit.

Considering that the diagnosis of POP may be difficult because of the frequent occurrence of fever, hypoxaemia or abnormal chest radiograph after lung resection in patients who do not have POP, the pragmatic attitude that POP must finally be diagnosed (or ruled out) on the basis of clinical, radiological and laboratory investigations seems to be justified. The next step is prompt antibiotic therapy, even in the absence of microbiological documentation.

Operation of a cavitating tumour

The operation of a cavitating tumour is a common situation in practice. Cavitating lung cancer is a true source of infection that may cause symptoms and delay of the surgical treatment. In the majority of cases, the cavitation arises from tumour necrosis [7], but can also occur as a result of bacterial colonisation or growth in the necrotic centre of tumours [8].

There are few data about this type of infection. In a study by KACPRZAK *et al.* [9] of 1148 patients who underwent pneumonectomy during an 8-year period, intra-operative infection occurred in

four (5.3%) out of 76 patients. Post-operative pleural empyema occurred in 76 (6.65%) patients, with bronchopleural fistula as a cause of empyema in three-quarters of these patients [9].

Fever is common in patients with primary lung cancer, with a reported incidence of 21.1% [10], and is usually caused by obstructive pneumonitis [11] or abscess. However, current imaging techniques are usually unreliable in differentiating in situ infection from necrosis in cavitating lung tumours.

Finding an optimal antimicrobial regime in these patients depends on bacteriological diagnosis, and several techniques of obtaining tissue cultures are available, with those performed during bronchoscopy being the most commonly used.

Ultrasound-guided transthoracic aspiration was also reported to be effective and even superior compared with biopsies performed under either fluoroscopy or computed tomography (CT), as it can be performed at the bedside, allows real-time monitoring, and costs less than CT and fluoroscopy [12]; it also minimises the risk of haemoptysis and haemothorax. In a recent study [13] of 22 patients who underwent ultrasound-guided transthoracic aspiration for bacterial, fungal and mycobacterial cultures, micro-organisms were isolated from six out of seven febrile patients and one out of 15 nonfebrile patients. In this series [13], the obtained culture results led to adjustment of the antibiotic regimen in five out of six febrile patients, previously treated with empirical agents. Initiation of individualised antimicrobial treatment led to the improvement of their clinical condition.

In the aforementioned study of 22 patients [13], six isolates were aerobic Gram-negative bacteria, one aerobic Gram-positive coccus and one *Mycobacterium*, with only one anaerobe isolated. Such a finding differs from previous reports [14], where 63% of isolates from lung abscesses were anaerobes and only 12 (19%) out of 65 isolates were Gram-negative bacilli. Similar results were obtained in studies performed by GRINAN *et al.* [15] and BARTLETT *et al.* [16]. These differences can be in part explained by the fact that the majority of patients in these reports [15, 16] had primary lung abscesses, while only a minority had underlying lung carcinoma. Furthermore, four out of six febrile patients who had positive results on lung aspirate cultures had received antimicrobial treatment, with coverage of anaerobic pathogens, before transthoracic aspiration.

Infection should be fully controlled before the operation, but this is not always possible, and febrile episodes may persist despite appropriate antibiotic treatment until surgical removal of the tumour (fig. 1).

In order to prevent intra-operative contamination, extrapleural liberation of the tumour from the chest wall is mandatory. This is particularly important in patients undergoing a pneumonectomy (fig. 1), given the high risk of post-operative empyema after intra-operative contamination of the pleural cavity. The same approach is also used in patients undergoing a lobectomy, with cavitating tumours sometimes occupying almost the entire affected lobe (fig. 2).

In case of involvement of the chest wall by the cavitating tumour, *en bloc* resection of the chest wall together with lung resection is mandatory. Discontinuing resection, *i.e.* separation of the lung from the chest wall with subsequent lung and chest wall resection, should be avoided whenever possible.

Lung infection unrecognised before the operation

Infection may persist within the lungs without clear radiographic or clinical signs before the lung resection. Unless the removed specimen is dissected immediately after the operation, the infection within the removed part of the lung may remain unknown. In such a case, a prolonged fever of unclear cause may ensue post-operatively, with analysis of the removed specimen revealing a suppurated lung cancer. In some patients, such tumours may be the true cause of staphylococcal infection with pneumatocele formation, sometimes giving the aspect of hydroaeric intrapulmonary or intrapleural collections (fig. 3).

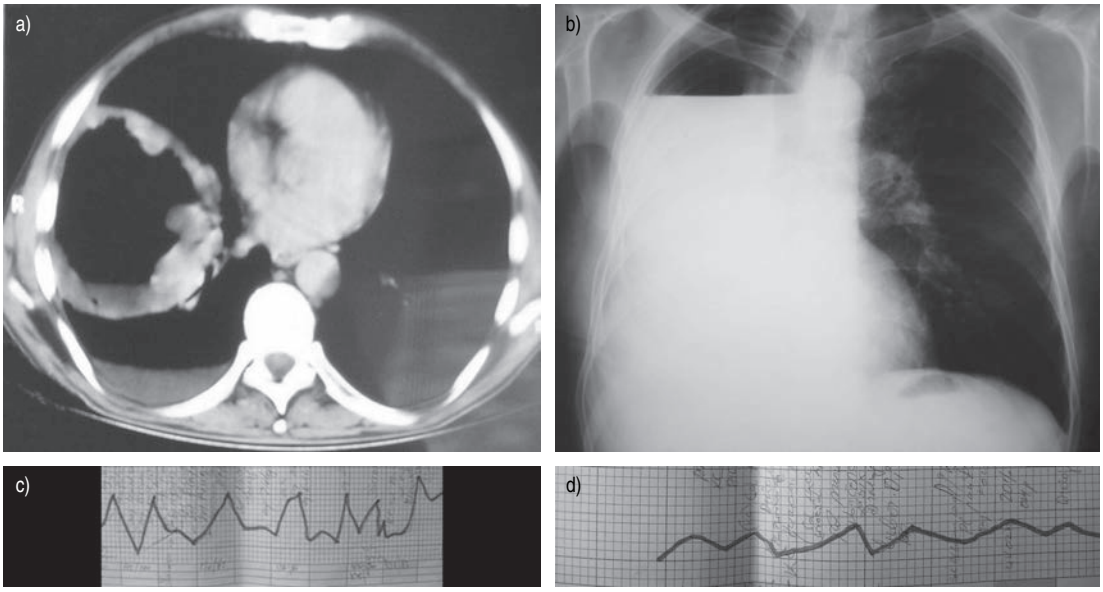


Figure 1. Necrotic lung cancer associated with a high febrility. a and c) On admission, a right-sided necrotic tumour causes a high febrility. b and d) No febrility can be seen after pneumonectomy.

For the prevention of complications in the case of intrapulmonary infection and the recognition of such a type of infection (*i.e.* white blood cells count, foetor ex ore and malaise), bacteriological confirmation and antibiotic prophylaxis are of utmost importance. During the operation, avoidance of spillage of intrabronchial secretions is very important. In the case of evident intra-operative contamination, some of the procedures for bronchial stump coverage should be performed together with lavage of the pleural space with an antiseptic solution.

Lung resection after pleural empyema

Unlike post-operative pleural empyema, which represents either the leading or second most frequent form of empyema in adults, pleural empyema as a complication of the natural course of lung cancer occurs less frequently. The latter is also less frequent than empyema occurring during and after chemo/radiation therapy in patients with unresectable lung cancer. The existence of

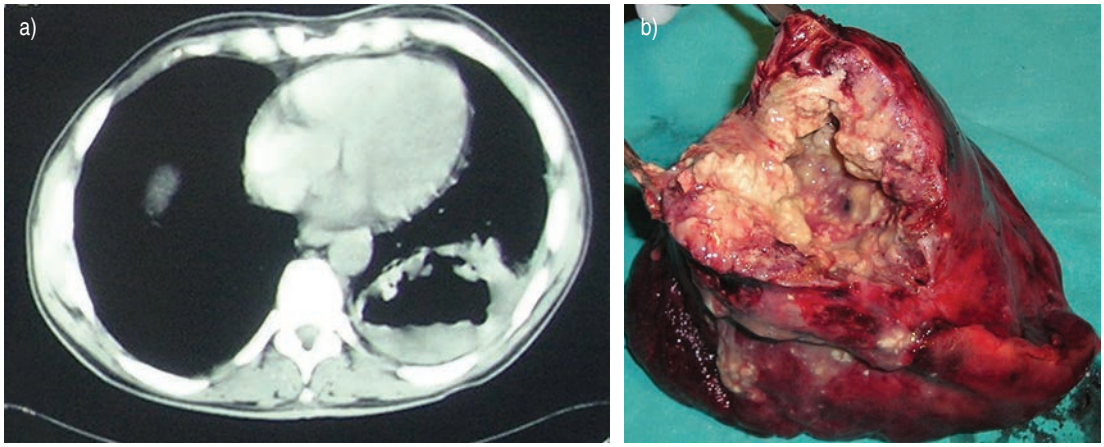


Figure 2. a) Cavitating tumour occupying a large part of the lobe. b) Operative specimen after lobectomy.

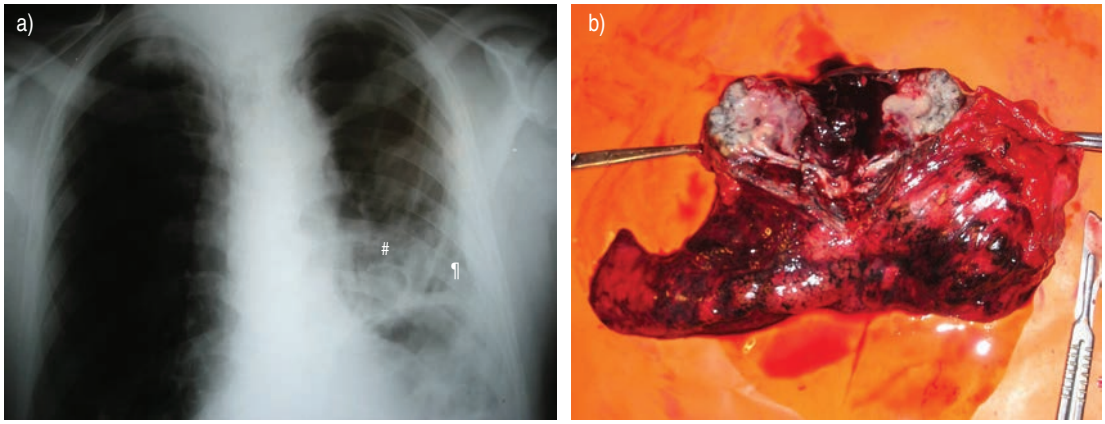


Figure 3. a) Staphylococcal infection after lobectomy. #: pneumatocele; ¶: diaphragm elevation after lobectomy. b) Operative specimen showing a cavitating tumour with fetid infection within the removed lobe.

pleural empyema does not always exclude a lung resection, but lung resection for lung cancer after a previously healed empyema may be justified only if a potentially curative resection is anticipated.

During the period 1970–1975, the association of pleural empyema with malignant disease was <3% (approximately one-third being associated with lung cancer) [17], whilst during the period 1980–1990, the association was 10%. This association increased to 22% in 1994, with 80% representing lung cancer [18]. Immunosupression with or without pneumopathy located distally from the obstruction is a possible explanation; the same explanation can be used for empyema in the presence of a contralateral tumour [19].

Mortality of empyema associated with malignant disease is 60–80% independent of pathogenesis [20]. Between 1970 and 1980, Gram-positive bacteria (*e.g. Staphylococcus aureus*) were the dominant causative micro-organisms. This trend remained unchanged between 1984 and 1988, but the more recent time period has been characterised by mixed infection with involvement of two or three bacterial strains and with an increase in Gram-negative bacteria.

There are two groups of patients with nonsmall cell lung cancer and associated pleural empyema who may be candidates for surgical treatment: 1) patients with empyema unrecognised before the operation; and 2) patients with empyema recognised and treated before the operation.

The first situation is rare in practice and relates to localised empyema adjacent to the necrotic and suppurated tumour, making it difficult to differentiate tumour mass from empyema. The same type of intra-operative contamination can ensue due to the existence of localised infected collections as a consequence of a localised intrapleural suppuration unrecognised and untreated pre-operatively. If the entire lung atelectasis is a dominant CT finding, it may mimic the associated collection of liquid (fig. 4). This collection may be unforeseen, even on CT, depending on the distance between two successive sequences. Intrapleural contamination occurs during the lung liberation of firm and diffuse adhesions. In this situation, the operative field is contaminated, the probability of post-operative empyema is high and the chance of post-operative adjuvant treatment is minimal.

In patients with pleural empyema recognised before the operation, diagnosis of lung cancer may be performed before, during or after empyema treatment. In these patients, the operative field is potentially contaminated.

In one of the rare published studies concerning this problem (only 18 patients in a 12-year period), operative mortality was 0% in nine patients (eight pneumonectomies and one lobectomy), with two post-operative empyemas. One patient survived for 5 years [21].

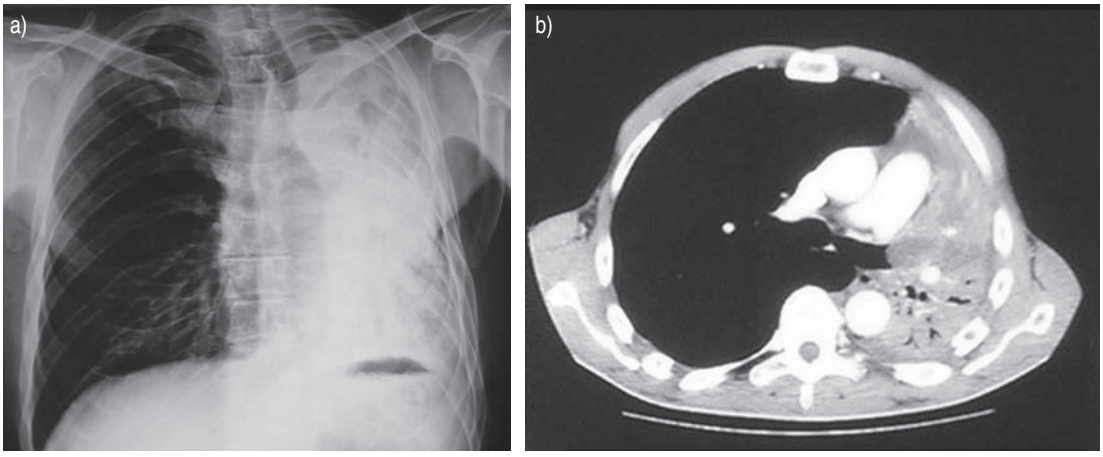


Figure 4. Intrapleural purulent liquid collection mimicked by the atelectatic lung. a) Pre-operative posterior-anterior radiography with a whole lung atelectasis as a dominant finding. b) Pre-operative computed tomography is also not suggestive of mimicked intrapleural liquid collection.

In another series of four pneumonectomies following previously treated pleural empyema, operative mortality was 0%, with two post-operative empyemas (one patient with diabetes) [22].

There are two possible situations determining a surgical approach after empyema has been treated and healed. The first, more favourable situation exists in patients in whom a good cleavage exists between the lung and chest wall, enabling intrapleural operation (fig. 5). In the patient presented in figure 5, empyema was treated by chest tube aspiration. It is difficult to anticipate with certainty such a situation before thoracotomy. Although no signs of intrapleural contamination may be present, these patients should be protected with more potent antibiotics than after pneumonectomy without previous empyema.

Another situation exists if the residual empyema sac persists after treatment, requiring extrapleural operation. This may be the case in patients undergoing either a pneumonectomy (fig. 6) or a lobectomy (fig. 7).

When considering the extent of such surgery, especially after extrapleural pneumonectomy, it should be mentioned that, in these patients, post-operative adjuvant therapy may not be possible due to the prolonged period of recovery and risk of complications. However, as already mentioned, such patients should not be automatically rejected from surgery, regardless of the severity of the

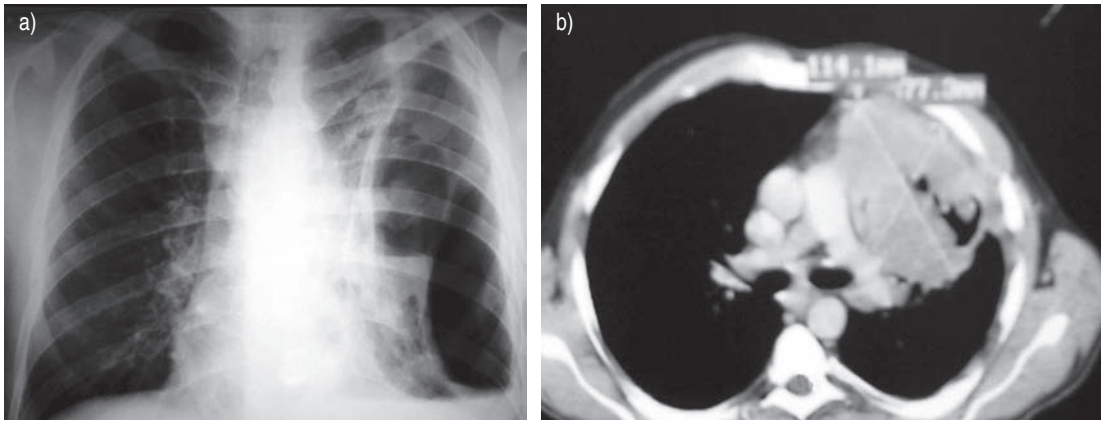


Figure 5. Pneumonectomy after a healed pleural empyema. a) On admission, before the chest tube insertion, and b) after healing of empyema. The local tumour spread requires a pneumonectomy.

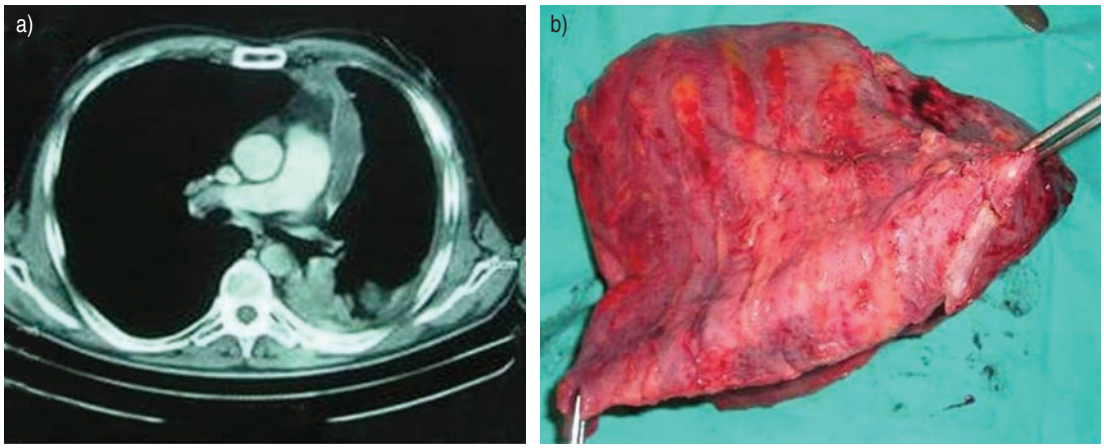


Figure 6. Pleuropneumonectomy after induction computed tomography (CT) and pleural empyema. a) CT before surgery, after healing of the empyema (repeated thoracentheses); a small residual collection exists paramediastinally. b) The operative specimen from the left lung with the overlying parietal pleura (showing visible rib impressions).

empyema, especially if lobectomy is anticipated, as presented in figure 7. In this patient, a putrid empyema occurred during the natural course of an untreated right-sided lung cancer. As shown in figure 7, almost complete lung expansion after chest tube insertion indicates the possibility of the empyema healing and subsequent surgery. In this situation, 3–4 weeks of active aspiration, combined with local and parenteral antibiotics with two or three drugs targetted at the pleural fluid cultures, is usually inevitable in order to achieve full lung expansion and control of infection [23]. However, due to the limited literature data on this subject, this aspect still remains controversial.

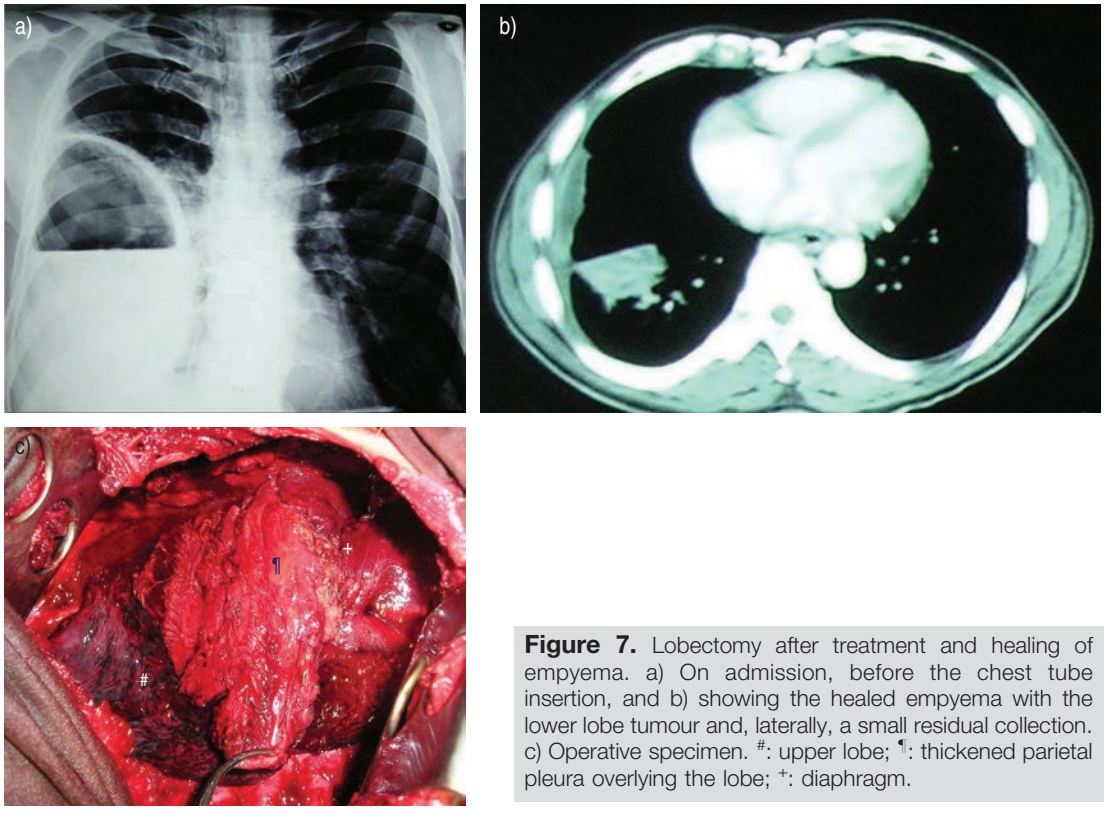


Figure 7. Lobectomy after treatment and healing of empyema. a) On admission, before the chest tube insertion, and b) showing the healed empyema with the lower lobe tumour and, laterally, a small residual collection. c) Operative specimen. #: upper lobe; ¶: thickened parietal pleura overlying the lobe; +: diaphragm.

Pleural fluid analysis immediately after chest tube insertion (or after thoracentheses, if the treatment is in the form of repeated thoracentheses) is mandatory. Surgical treatment should be offered only to younger patients with a good general condition.

In brief, lung resection for lung cancer after previous pleural empyema may be potentially curative. The main problems that need to be solved are as follows and will be discussed hereafter: 1) delay in initiation of lung cancer treatment in order to heal empyema and obliterate the pleural space; 2) adjuvant treatment may not always be possible; and 3) pneumonectomy is associated with increased operative morbidity.

Delay in initiation of lung cancer treatment in order to heal empyema and obliterate the pleural space

Although obliteration of the pleural space can be achieved in 2 weeks after the onset of empyema, this time interval may sometimes exceed 1–1.5 months. Such an approach may be justified only in the presence of clear signs that the lung has a capacity either to fully obliterate the pleural space or to achieve nearly full obliteration with well-defined residual cavities that may be fully mobilised and removed during the operation, thus avoiding spillage of the infected liquid. In this situation, when a potentially curative operation is anticipated, the delay seems to be appropriate, because the lung resection itself will be more beneficial compared with either chemo- or radiation therapy alone. Furthermore, successful surgery may be followed by adjuvant therapy.

The radiographic aspect of a partially expanded lung with a persistent air leak represents a major risk for post-operative major complications, even after lobectomy; the risk of eventual pneumonectomy is unacceptable in this situation.

Adjuvant treatment may not always be possible

Even without pre-operative empyema, the impossibility of receiving a full dose of adjuvant treatment after pneumonectomy should not be neglected. In the Cancer and Leukemia Group B trial 9633 report [24], 55% of patients received full-dose chemotherapy, whilst in the Intergroup JBR.10 trial [25], 45% of patients had at least one dose delay. In another report, ~34% of patients received full-dose chemotherapy [26].

Considering the decreased lung elasticity after previous empyema treatment, the possibility of an air leak requiring prolonged aspiration occurs more frequently than usual. Furthermore, the general condition of patients who are already exhausted by previous empyema treatment may not be optimal and, thus, some of these patients may not tolerate the full course of adjuvant treatment or, indeed, may not tolerate treatment at all. This drawback is balanced, however, by the potential benefit of surgery.

Pneumonectomy is associated with increased operative morbidity

It should always be remembered that pneumonectomy is associated with increased operative morbidity, and some form of bronchial stump protection should be performed whenever possible, especially for right-sided operations. It is of particular importance to prevent a post-operative infection by administering intrapleural antibiotic application from the 2–3 days post-operatively, even in presence of an uneventful clinical course. In any event, this kind of surgery requires a highly skilled and experienced team.

Conclusions

To conclude, the outcome of surgical lung cancer treatment in the presence of intrapulmonary infection does not depend only on surgical skills, but also on appropriate pre-operative and

post-operative medical treatment. Knowledge of the correlation between pre-operative colonisation and the type of post-operative complications that might occur is of utmost importance.

Lung resection for lung cancer after previous pleural empyema represents a challenging operation from all aspects. However, it does not represent an absolute contraindication for surgery.

Statement of Interest

None declared.

References

1. Sok M, Dragas AZ, Erzen J, *et al.* Sources of pathogens causing pleuropulmonary infections after lung cancer resection. *Eur J Cardiothorac Surg* 2002; 22: 23–27.
2. Ioanas M, Angrill J, Baldo X, *et al.* Bronchial bacterial colonization in patients with resectable lung carcinoma. *Eur Respir J* 2002; 19: 326–332.
3. Schussler O, Alifano M, Dermine H, *et al.* Postoperative pneumonia after major lung resection. *Am J Respir Crit Care Med* 2006; 173: 1161–1169.
4. Schussler O, Dermine H, Alifano M, *et al.* Should we change antibiotic prophylaxis for lung surgery? Postoperative pneumonia is the critical issue. *Ann Thorac Surg* 2008; 86: 1727–1733.
5. Yamada Y, Sekine Y, Suzuki H, *et al.* Trends of bacterial colonization and the risk of postoperative pneumonia in lung cancer patients with chronic obstructive pulmonary disease. *Eur J Cardiothorac Surg* 2010; 37: 752–757.
6. Sethi S, Evans N, Grant BJ, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
7. Chaudhuri MR. Primary pulmonary cavitating carcinomas. *Thorax* 1973; 28: 354–366.
8. Pan JF, Yang PC, Chang DB, *et al.* Needle aspiration biopsy of malignant lung masses with necrotic centers: improved sensitivity with ultrasonic guidance. *Chest* 1993; 103: 1452–1456.
9. Kacprzak G, Marciniak M, Addae-Boateng E, *et al.* Causes and management of postpneumonectomy empyemas: our experience. *Eur J Cardiothorac Surg* 2004; 26: 498–502.
10. Rassam JW, Anderson G. Incidence of paramalignant disorders in bronchogenic carcinoma. *Thorax* 1975; 30: 86–90.
11. Liaw YS, Yang PC, Wu ZG, *et al.* The bacteriology of obstructive pneumonitis: a prospective study using ultrasound-guided transthoracic needle aspiration. *Am J Respir Crit Care Med* 1994; 149: 1648–1653.
12. Yang PC, Luh KT, Sheu JC, *et al.* Peripheral pulmonary lesion: ultrasonography and ultrasonically guided aspiration biopsy. *Radiology* 1985; 155: 451–456.
13. Liao W-Y, Liaw YS, Wang HC, *et al.* Bacteriology of infected cavitating lung tumor. *Am J Respir Crit Care Med* 2000; 161: 1750–1753.
14. Yang PC, Luh KT, Lee YC, *et al.* Lung abscess: US examination and US-guided transthoracic aspiration. *Radiology* 1991; 180: 171–175.
15. Grinan NP, Lucena FM, Romero JV, *et al.* Yield of percutaneous needle lung aspiration in lung abscess. *Chest* 1990; 97: 69–74.
16. Bartlett JG, Gorbach SL, Tally FP, *et al.* The bacteriology and treatment of primary lung abscess. *Am Rev Respir Dis* 1974; 109: 510–518.
17. Vianna NJ. Nontuberculous bacterial empyema in patients with and without underlying diseases. *JAMA* 1971; 215: 69–75.
18. Koike T, Takizawa T, Akamatsu H, *et al.* Resection of lung cancer complicated by pleural empyema. *Nippon Kyobu Shikkan Gakkai Zasshi* 1995; 33: 670–673.
19. Molina R, Baro T, Torne J, *et al.* Empyema caused by *Kingella denitrificans* and *Peptostreptococcus* spp. in a patient with bronchogenic carcinoma. *Eur Respir J* 1988; 1: 870–871.
20. Benfield GFA. Recent trends in empyema thoracis. *Br J Dis Chest* 1981; 75: 358–366.
21. Riquet M, Hubsch JP, Le Pimpec Barthes F, *et al.* Pleuresies purulentes et cancer du poumon. [Purulent pleurisy and lung cancer. Non-iatrogenic forms and therapeutic management.]. *Rev Mal Respir* 1999; 16: 817–822.
22. Subotić D, Mandarić D, Atanasijadis N, *et al.* Pneumonectomy due to bronchus carcinoma after pleural empyema. *Serbian Arch Med* 2002; 130: 208–212.
23. Harada M, Yoshida J, Yokose T, *et al.* Surgical management of primary lung cancer in an elderly patient with preoperative empyema. *Jpn J Clin Oncol* 1999; 29: 571–575.
24. Strauss GM, Herndon J, Maddaus MA, *et al.* Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage 1B non-small-cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633. *J Clin Oncol* 2004; 22: 621s.
25. Winton T, Livingston R, Johnson D, *et al.* Vinorelbine plus cisplatin *vs.* observation in resected non-small-cell lung cancer. *N Engl J Med* 2005; 352: 2589–2597.
26. Scagliotti GV, Fossati R, Torri V, *et al.* Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003; 95: 1453–1461.

Chapter 15

Dealing with infection after thoracic surgical procedures

Emilio Canalis[*], *Danail Petrov*[#] *and Antoni Torres*[¶]

SUMMARY: Irrespective of the extent of resection, post-operative pleural infection is a dominant cause of operative morbidity and mortality. Two major causes of infection are prolonged air leak and bronchopleural fistula (BPF) after pneumonectomy. Prolonged air leaks occur in around 33% of patients after a lobectomy. As this inevitably leads to pleural empyema, the treatment goal is to obliterate the pleural space. If empyema occurs, chest tube aspiration will obliterate the pleural space after 7–14 days, unless a BPF exists. Prevention of the air leak can be achieved by an appropriate technique or by the use of sealants. After pneumonectomy, pleural empyema and BPF are associated in up to 80% of patients and mortality is high (total of 10–20%; up to 50% mortality with BPF). Chest tube aspiration may lead to a stable condition with a chronic small-sized fistula that can be tolerated for years. Definitive treatment includes wide opening of the pleural cavity with muscle transposition for fistula closure. Fistulae may be closed through a trans-sternal trans-pericardial approach as well.

[*]Thoracic Surgery Service, Hospital Universitari Joan XXIII, URV, IISPV, Tarragona, and [¶]Hospital Clínic, UB, Barcelona, Spain.
[#]Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases, Medical University, Sofia, Bulgaria.

Correspondence: E. Canalis, Hospital Universitari Joan XXIII, C/ Doctor Mallafré Guasch 4, 43007 Tarragona, Spain. Email: emilio.canalis@urv.cat

Eur Respir Monogr 2013; 61: 171–180.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10041712
Print ISBN: 978-1-84984-036-1
Online ISBN: 978-1-84984-037-8
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Compared with the situation 20 years ago, there has been a decrease in operative morbidity and mortality after lung resections, independent of the extent of resection. After lobectomy, operative mortality usually does not exceed 2%. Although operative mortality after pneumonectomy should not exceed 5%, the reported mortality rate is 5–10% [1]. The reported mortality rates after sleeve lobectomy, used as an alternative to pneumonectomy, are not significantly different from those after standard lobectomy, with long-term survival comparable to that after pneumonectomy [2, 3]. Even after sleeve pneumonectomy, operative mortality should not exceed 10%.

Independently of the extent of resection, post-operative pleural infection is a dominant cause of operative morbidity and mortality. There are two major causes of infection after thoracic surgical procedures: 1) prolonged air leak after lobectomy, and 2) bronchopleural fistula (BPF) after pneumonectomy.

Prolonged air leak

Alveolo-pleural fistula, the leading cause of a prolonged air leak, occurs in around 33% of patients with a lobectomy. The wide range of the reported incidence of this complication (3–70%) is due to different definitions of the air leak: in some studies any air leak is regarded as a complication, while in other studies the authors consider the air leak significant only if its duration exceeds 7 days. This type of air leak occurs in 15–25% of operated patients, representing the main cause of longer hospital stay, because of the need for chest tube aspiration [4]. Risk factors for the occurrence of this complication are low predicted post-operative forced expiratory volume in 1 second (FEV_1), pleural adhesions, upper lobectomy and bilobectomy, and these were identified in a prospective study on 588 patients with a lobectomy [5]. In another study on 688 patients, in which air leak up to the fourth post-operative day was regarded as a complication, male sex, steroid treatment, persistent pneumothorax and lobectomy were identified as unfavourable prognostic factors [6]. Although several studies have demonstrated the causative relationship between air leak and poor lung function (low FEV_1 and FEV_1/forced vital capacity), diabetes, older age, male sex and adhesions [7–9], there are also studies that have not confirmed such a relationship, while at the same time identifying left lower lobectomy as the least frequently complicated by air leaks [10].

The increased use of induction treatment, by decreasing the lung elasticity, can also lead to prolonged lung expansion (fig. 1).

As a prolonged air leak after a lobectomy inevitably leads to pleural empyema, the treatment rationale is based on the need to obliterate the pleural space as much as possible and as soon as possible. The first step is to replace the thick calibre operative chest tubes with narrower ones (16–20 French), inserted either through the apical part of the chest (as presented on figure 1), or through other chest wall areas, according to need. Usually one such tube suffices. This procedure, unless postponed after post-operative day 7–10, in the absence of BPF, helps to avoid pleural empyema in the great majority of patients. Even if empyema occurs, the pleural space will become obliterated after 7–14 days, unless BPF exists or occurs during the treatment.

Although the treatment of pleural empyema after a lobectomy is usually not a life-threatening situation, given the increasing number of patients with major comorbidity, prevention of the air leak is of utmost importance in practice. Air leak prevention begins with appropriate surgical technique, with the use of staplers whenever possible in the presence of less developed or missing fissures. Gentle phrenic nerve clamping, aimed at temporarily reducing the size of the pleural space, is a frequently performed manoeuvre. Creating a "pleural tent", by detaching the apical parietal pleura from the chest wall, although suggested by some authors, is not widely accepted. Additionally, different types of sealants are also in use, like fibrin glue [11–13], polyethylene glycol-based substances and patches coated with fibrinogen and thrombin [14].

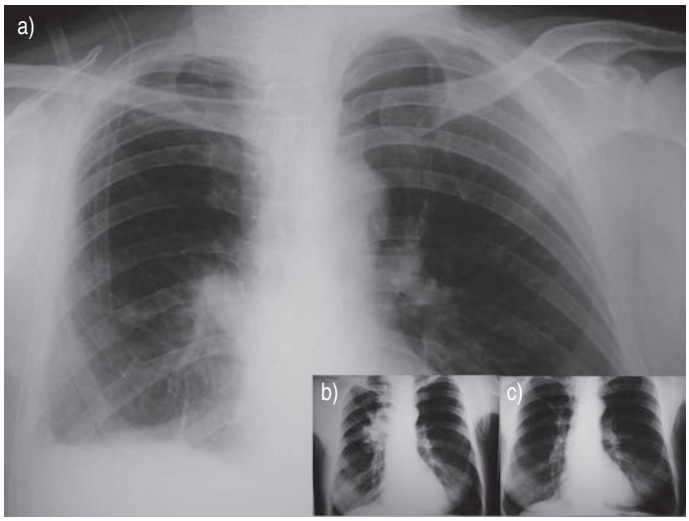


Figure 1. Lobectomy after induction chemotherapy. a) Chest tube aspiration for prolonged air leak. Radiographic aspect b) before and c) after induction chemotherapy.

As a treatment option for existing air leaks, intrapleural application of autologous blood can also be

used. In a study with air leak in 6.9% of operated patients, the leak was resolved one day after the application in 58.6% of patients. The duration of the air leak in the group with autologous blood application was 5 days, *versus* 11 days in the control group ($p<0.001$) [15].

Infectious complications after pneumonectomy

Apart from the standard risk factors for operative morbidity after lung resections, such as respiratory and cardiovascular comorbidity, the leading causes of post-operative morbidity after pneumonectomy are pleural empyema and BPF.

Post-pneumonectomy empyema is a rare but serious complication with an incidence rate of 4.4–16% [16–18]. Approximately 75% of post-pneumonectomy empyema cases occur within the first 3 months of pneumonectomy, but it may appear even years after the procedure [19, 20]. In up to 80% of patients, post-pneumonectomy empyema is associated with BPF [16]. Despite the use of various therapeutic approaches and techniques during the last five decades, successful therapy remains difficult and is often associated with high mortality (total of 10-20%; up to 50% mortality in cases with BPF), morbidity and prolonged hospital stay [21–23].

The occurrence of post-pneumonectomy empyema is adversely affected by different factors, especially benign disease and lower diffusing capacity of the lung for carbon monoxide ($p=0.001$), followed by lower FEV_1. Lower pre-operative serum haemoglobin, right pneumonectomy, bronchial stump reinforcement, completion pneumonectomy, timing of chest tube removal and the amount of blood transfusions also represent contributive factors. Additional major risk factors for post-pneumonectomy empyema are immunosuppression and neoadjuvant or adjuvant chemotherapy [24, 25]. If a pneumonectomy, especially right-sided, is anticipated after induction chemotherapy and/or radiation therapy, some form of bronchial stump protection should be used (fig. 2).

The reasons for BPF occurrence related to the operative technique are threefold. First, suture insufficiency causes a fistula that becomes evident immediately after the operation or during the first 24–48 h post-operatively. Secondly, excessive bronchial dissection leads to devascularisation and fistula that becomes evident 7–14 days after the operation. Thirdly, bronchial division through the diseased tissue leads to BPF that becomes evident up to 1 month after surgery.

Post-operative irradiation therapy may cause the BPF during or after completion of the treatment. Secondary fistulae may be caused by post-operative pleural empyema, especially in the elderly or in patients unfit for surgery. This type of fistula did not exist before the empyema occurrence.

BPF occurs in around 1.6% of all thoracic surgical procedures and is significantly more frequent after

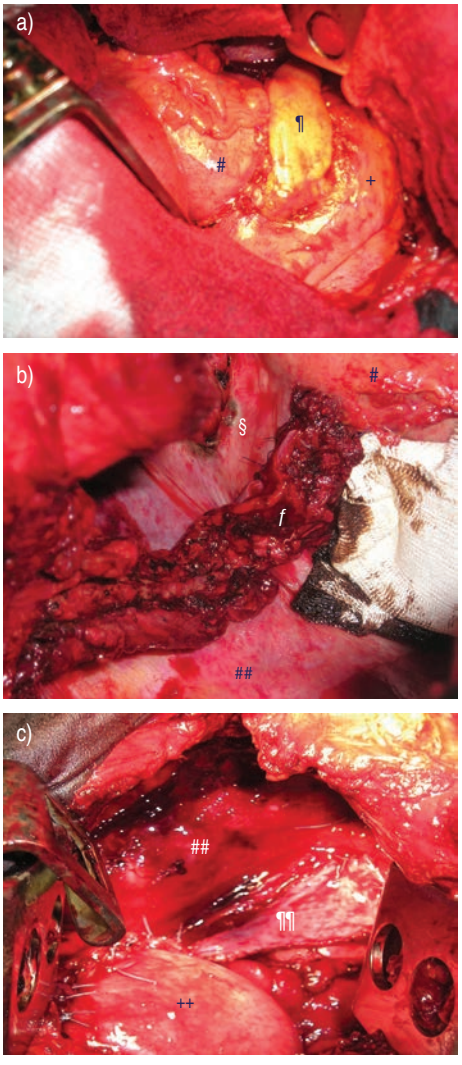


Figure 2. Bronchial stump protection after pneumonectomy. a) Pericardial fat pad, b) intercostal muscle flap, and c) diaphragmal flap. #: pericardium; ¶: pericardial fat; +: aorta; §: azygos vein; *f*: muscle flap; ##: spine; ¶¶: flap; ++: diaphragm.

Table 1. Operative morbidity and mortality after standard pneumonectomy

First author [ref.]	Year	Patients n	Operative mortality %	Operative morbidity %	BPF %	Diagnosis
Bernard [32]	2001	639	7	43.2	0.6	Lung cancer
Algar [33]	2003	242	5.4	59	5.4	Lung cancer
Borri [34]	2007	47¶	4.2	17	1.1	Lung cancer
Leo [35]	2007	35+	11.4	54.2	NR	Lung cancer
Powell [36]#	2009	312	5.4	31.7	NR	Lung cancer
Stolz [37]	2011	310	5.5	27.1	3.8	Lung cancer
Petrella [38]	2011	154	6	42.2	NR	Lung cancer
Blyth [39]	2000	155	1.2	1.9	23	Inflammatory
Owen [40]	2012	32	6	38	0	Benign

BPF: bronchopleural fistula; NR: not reported. #: United Kingdom pneumonectomy outcome study (UKPOS); ¶: extended pneumonectomies; +: age >70 years.

pneumonectomy than after lobectomy. Before the use of staplers, BPF occurred in up to 15% of patients after a pneumonectomy. The reported incidence is 5–10% in recent years, although it was also demonstrated that it was possible to reduce it to approximately 2% with an appropriate bronchial stump protection [26].

BPF is also among the leading causes of death after sleeve pneumonectomy, especially if the resected tracheobronchial segment exceeds 4 cm. Even after this extensive operation, operative mortality has gradually decreased from 31% in the early reports from the 1970s [27, 28], through the still high 34% mortality rate in the mid-1990s [29], to less than 10% in some later series in the late 1990s [30]. It seems that 15–17% operative mortality is reasonable, bearing in mind the specificity of this procedure [31].

The treatment outcomes and complications after standard and sleeve pneumonectomy are summarised in tables 1 and 2.

Treatment of post-pneumonectomy empyema and BPF

Emergency tube thoracostomy drainage should be the first step in the acute phase of the empyema and patients should be instructed to keep the operative side dependent until the empyema can be drained to prevent spillage into the remaining lung. Bronchoscopy is then performed to confirm or rule out bronchial stump insufficiency. Operative mortality is mostly secondary to respiratory failure from pulmonary infection caused by spillage of purulent liquid across the BPF into the contralateral lung. Sterilisation, debridement, closure of present BPF and obliteration of pleural cavity (antibiotic plombage, muscle and omental pedicle flaps or thoracoplasty) follow the first step.

There is no universally appropriate treatment, so management depends upon the post-pneumonectomy empyema stage, presence of bronchial stump insufficiency and the patient's

Table 2. Survival and complications after sleeve pneumonectomy

First author [ref.]	Year	Patients n	Operative mortality %	Operative morbidity %	5-year survival %
Tsuchiya [41]	1990	20	15	40	59#
Mathisen [42]	1991	37	8	64.8	19
Dartevelle [43]	1995	55	7.2	10.9	40
Roviaro [44]	2001	49	8.2	10.2	24.5
Porhanov [45]	2002	191	17.8	24	24.7
Subotich [46]	2006	42	16.6	35.7	35

#: at 2 years.

general condition. In the absence of BPF, aggressive surgery is a questionable option because of its high morbidity and because it does not always prevent recurrences.

Pleural cavity drainage alone is considered a palliative procedure. As a definitive treatment it includes irrigation by an additional apical drain and endoscopic closure of small bronchial fistulae by fibrin glue if necessary. The shortcomings of the method are prolonged treatment, discomfort caused by the intrapleural drain, uncertain cavity obliteration and chest deformity.

In 1963, CLAGETT and GERACI [47] introduced a two-stage procedure that consisted of 1) open pleural drainage (open-window thoracostomy (OWT)) with pleural space cleaning and eventually obliteration by daily dressing changes through the thoracostomy (4–6 weeks), followed by 2) obliteration of the pleural cavity with debridement antibiotic solution at the time of chest wall closure. The procedure was successful in 88% of cases (n=14), but resulted in prolonged hospitalisation and significant morbidity. Failure was often the result of persistent or recurrent BPF [48].

In an attempt to overcome these failures, PAIROLERO *et al.* [49] modified the Clagett procedure with initial bronchial stump reinforcement and decreased the size of the pleural cavity by transposition of well-vascularised extrathoracic muscle as an intermediate step before obliteration of the pleural cavity with antibiotic solution. The success of the Pairolero modification (n=28) was 83.9%; however, surgical re-interventions were numerous and the hospitalisation time long [49].

In their article on the Mayo Clinic experience, ZAHEER *et al.* [50] reported that the initial closure of the chest before hospital discharge failed in 19% of patients (n= 84) and after a second Clagett procedure, 88% of all patients had their chest walls successfully closed. Eight (9.5%) patients had to live with a permanent thoracic wall defect. BPF healing was achieved in 55 patients. However, the recurrence rate after the first attempt was 18%, and that after the second attempt was 5%. Peri-operative mortality in their series was 7.1%. Late onset of post-pneumonectomy empyema and immediate thoracostomy creation [51], as well as age under 65 years [50], are significant predictors of OWT closure.

As the process of obliteration of pleural space after OWT alone may take up to 2 years, several authors have suggested the need for further surgery to obliterate the pleural space [52, 53]. Different extrathoracic muscle or omental transposition was used to obliterate the pleural space and, at the same time, to close a possibly associated BPF after OWT. It has been reported that both omentum and muscle flaps may play an important role in infection control. Furthermore, both stimulate neoangiogenesis of ischaemic bronchial stumps. Using intrathoracic muscular or omental transposition it should be kept in mind that no residual space should be left and that a sufficient number of flaps must be available to fill any space. The extrathoracic muscle flap advantages are their reliable blood supply, ability to reach almost any part of the pleural space and sufficient volume to fill the cavity [54]. However, functional impairment may contraindicate this procedure in debilitated patients, following radiotherapy and posterolateral thoracotomy.

Obliteration of the cavity should be carried out at least 3 months after an operation for benign disease. The arguments against operative closure of OWT within 2 years of post-pneumonectomy empyema in lung cancer patients are the acceptable probability of spontaneous resolution and the risk of recurrent disease [55]. In this setting, it is recommended to wait no less than 6 months between performing and closing the OWT [56].

The omental pedicle flap maintains a rich blood supply and lymph circulation, accelerates vascularisation due to angiogenic factors, promotes drug transfer in the peripheral blood to affected areas, has potent anti-inflammatory and self-cleansing effects, and sufficient volume. The procedure is minimally invasive and simple [18, 57]. Omentoplasty could be applied in high-risk patients, in patients with a history of radiotherapy and posterolateral thoracotomy, and especially in cases with BPF [58].

Closure of BPF is of paramount importance in post-pneumonectomy empyema treatment. Different techniques depend on the type and size of the insufficiency. Endoscopic treatment of a

BPF that is <3 mm with various glues and sclerosing agents is minimally invasive and plays an essential role, especially in high-risk patients [59, 60].

Access to the stump could be achieved *via* the same pleural cavity, through the contralateral pleural cavity in the case of left stump fistula, and by means of transmediastinal video-assisted thoracoscopic surgery (VATS) application [61]. The advantages of trans-sternal trans-pericardial closure of BPF (Abruzzini technique) are avoidance of areas of infection, scarring in previous surgical fields, devascularised bronchus, and cosmetic and functional deformities of the thorax because of thoracoplasty. This technique is also an alternative in the management of persistent fistula after repair by other techniques [62]. The disadvantage of this method is that the residual empyema space is not dealt with at the same time as the closure of BPF and additional surgical procedures are needed. Several authors have performed carinal resection using the trans-sternal approach in cases in which a short, <5-mm bronchial stump was present [63–66]. SPAGGIARI *et al.* [67] developed a minimally invasive Abruzzini-like technique using three simultaneous approaches: cervical videomediastinoscopy, right anterior mediastinotomy and parasternal thoracoscopic port. Disadvantages of the older procedures for post-pneumonectomy empyema treatment are prolonged and very expensive treatment.

In patients with early post-pneumonectomy empyema associated with BPF, GHARAGOZLOO *et al.* [22] have reported a 100% success rate with shorter hospitalisation and decreased morbidity. Their Clagett procedure modification is based on emergency tube drainage followed by thoracotomy, debridement, bronchial stump resuture, and immediate chest cavity closure. Post-operative pleural irrigation and obliteration of the space by antibiotic solution constitute the final part of the treatment, but this approach should be considered only in a very selected subset of patients.

The accelerated Weder method might be considered an advancement of the Clagett procedure and leads to a high success rate of 97.3% with mean post-operative hospital stay of 17–18 days [68]. The therapy consisted of repeated open surgical debridement of the pleural cavity after achievement of general anaesthesia, a negative pressure wound therapy of the temporarily closed chest cavity filled with povidone-iodine-soaked towels, and continuous suction and systemic antimicrobial therapy. If present, BPF were closed and reinforced either with a muscle flap or the omentum. Finally, the pleural space was filled with an antibiotic solution and definitively closed. The procedure is repeated every 48 hours and usually a mean of 3.5 procedures are enough until the chest cavity is macroscopically clean. Finally, the pleural space is filled with an antibiotic solution and definitively closed.

Petrov recently introduced a video-assisted modification of the Weder procedure (n=3), which is carried out through a 4–5-cm minithoracotomy (D. Petrov, Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases, Sofia, Bulgaria; personal communication). The first session was carried out under general anaesthesia, which was improvised on the assumption that more extensive surgery might be required. A high thoracic epidural with preserved self-ventilation was the anaesthesia for the remaining sessions and for post-operative pain relief. The pleural cavity was never drained between sessions. Post-pneumonectomy empyema was successfully treated in all patients (three sessions needed), with mean hospital stay of 10.3 days followed by excellent long-term functional and cosmetic results.

One of the reasons for avoidance of VATS may be the fear of using VATS for a serious and potentially lethal complication and of overlooking infected tissues in the regions that are difficult to reach with the thoracoscope. However, there is no evidence that success relies on complete debridement of all infected tissues. If VATS fails to accomplish as thorough a pleural cleaning as does thoracotomy, it is often successful because the bacterial load and inflammatory exudates are reduced below a critical level, allowing the pleural space to recover.

In the report of HOLLAUS *et al.* [69], infected material was cleared by VATS, followed by post-operative antibiotic irrigation according to culture sensitivity *via* a single chest tube drainage twice a day (n=9). Empyema was considered eradicated if three subsequent cultures showed no bacterial growth. The mean hospital stay was 29 days. A thoracoscopic debridement without irrigation in

the post-operative course has also been described [70]. In the case of persistent infectious symptoms (27% recurrence rate), thoracoscopy was not repeated and an OWT was performed.

BAGAN *et al.* [71] described treatment that started with pleural cavity antibiotic irrigation for 10 days through two chest tubes twice a day. Pleural instillation of 250 000 IU streptokinase was performed 2 hours before the procedure, followed by VATS debridement under general anaesthesia and with a chest tube left in the thoracic cavity. This protocol provided satisfactory results in terms of hospital stay and number of sepsis recurrences.

ERNST and NIES [72] reported three post-pneumonectomy empyema patients treated with repeated thoracoscopic debridements and intermittent lavage with polyvinylpyrrolidine-iodine solution and streptokinase/streptodornase. Three to seven thoracoscopies under general anaesthesia were required to sterilise the pleural cavity. After a median follow-up of 14 months, all three patients were well and without any evidence of infection.

Petrov has also successfully performed repeated VATS debridements and lavage with povidone-iodine solution (n=4) *via* two ports, but only the first VATS debridement was under general anaesthesia (D. Petrov, Thoracic Surgery Division, Saint Sophia University Hospital for Pulmonary Diseases; personal communication). The following VATS procedures were carried out using epidural analgesia at the T6–8 interspace. Between the procedures the pleural cavity was filled with povidone-iodine solution (1:10), without intrathoracic tube drainage.

Several authors have suggested a limited thoracoplasty as an excellent therapeutic option for treating post-pneumonectomy empyema, avoiding multiple operations and the psychological drawbacks of prolonged hospitalisation or of definitive open drainage [73–76]. CORNET *et al.* [77] reported that 75% of their patients were able to work again. Andrews thoracoplasty allows a good control of infection with complete evacuation of the products of empyema under direct vision, an immediate closure of any bronchial fistula, a one-stage procedure, and a rapid and most often simple post-operative recovery [78]. This surgical procedure could be at least an alternative method to open thoracostomy whenever a secondary closure seems to be uncertain, or could be used in case of failure of other treatments. These results and the quality of life after this thoracopleuroplasty should support the rediscovery of this time-honoured procedure in properly selected patients.

In conclusion, post-pneumonectomy empyema treatment (usually by combination of methods) should be individually tailored for each and every case. The Clagett procedure and its modifications are safe and effective in pleural cavity obliteration. Extrathoracic muscle myoplasty is an excellent method for obliteration of post-pneumonectomy empyema cavity with BPF. Omentoplasty is an effective and safe procedure in selected cases of post-pneumonectomy empyema. VATS debridement can cure most patients with minor or no BPF and does not preclude more aggressive surgical management in case of failure or relapse.

Statement of Interest

A. Torres has received fees for consultancy from Astellas and Astra Zeneca.

References

1. Wahi R, McMurtrey MJ, DeCaro LF, *et al.* Determinants of perioperative morbidity and mortality after pneumonectomy. *Ann Thorac Surg* 1989; 48: 33–37.
2. Tedder M, Anstadt MP, Tedder SD, *et al.* Current morbidity, mortality, and survival after bronchoplastic procedures for malignancy. *Ann Thorac Surg* 1992; 54: 387–391.
3. Okada M, Yamagishi H, Satake S, *et al.* Survival related to lymph node involvement in lung cancer after sleeve lobectomy compared with pneumonectomy. *J Thorac Cardiovasc Surg* 2000; 119: 814–819.
4. Serra-Mitjans M, Belda-Sanchis J, Rami-Porta R. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer. *Cochrane Database Syst Rev* 2005; 3: CD003051.
5. Brunelli A, Monteverde M, Borri A, *et al.* Predictors of prolonged air leak after pulmonary lobectomy. *Ann Thorac Surg* 2004; 77: 1205–1210.

6. Cerfolio RJ. Recent advances in the treatment of air leaks. *Curr Opin Pulm Med* 2005; 11: 319–323.
7. Abolhoda A, Liu D, Brooks A, *et al.* Prolonged air leak following radical upper lobectomy: an analysis of incidence and possible risk factors. *Chest* 1998; 113: 1507–1510.
8. Hazelrigg SR, Nunchuck SK, LoCicero J 3rd. Video Assisted Thoracic Surgery Study Group data. *Ann Thorac Surg* 1993; 56: 1039–1043.
9. Isowa N, Hasegawa S, Bando T, *et al.* Preoperative risk factors for prolonged air leak following lobectomy or segmentectomy for primary lung cancer. *Eur J Cardiothorac Surg* 2002; 21: 951.
10. Okereke I, Murthy SC, Alster JM, *et al.* Characterization and importance of air leak after lobectomy. *Ann Thorac Surg* 2005; 79: 1167–1173.
11. Fabian T, Federico JA, Ponn RB. Fibrin glue in pulmonary resection: a prospective, randomized, blinded study. *Ann Thorac Surg* 2003; 75: 1587–1592.
12. Fleisher AG, Evans KG, Nelems B, *et al.* Effect of routine fibrin glue use on the duration of air leaks after lobectomy. *Ann Thorac Surg* 1990; 49: 133–134.
13. Wong K, Goldstraw P. Effect of fibrin glue in the reduction of postthoracotomy alveolar air leak. *Ann Thorac Surg* 1997; 64: 979–981.
14. Anegg U, Lindenmann J, Matzi V, *et al.* Efficiency of fleece-bound sealing (TachoSil) of air leaks in lung surgery: a prospective randomised trial. *Eur J Cardiothorac Surg* 2007; 31: 198–202.
15. Shackcloth MJ, Poullis M, Jackson M, *et al.* Intrapleural instillation of autologous blood in the treatment of prolonged air leak after lobectomy: a prospective randomized controlled trial. *Ann Thorac Surg* 2006; 82: 1052–1056.
16. Wong PS, Goldstraw P. Post-pneumonectomy empyema. *Eur J Cardiothorac Surg* 1994; 8: 345–349.
17. Deschamps C, Pairolero PC, Allen MS, *et al.* Management of postpneumonectomy empyema and bronchopleural fistula. *Chest Surg Clin N Am* 1996; 6: 519–527.
18. Schneiter D, Grodzki T, Lardinois D, *et al.* Accelerated treatment of postpneumonectomy empyema: a binational long-term study. *J Thorac Cardiovasc Surg* 2008; 136: 179–185.
19. Shamji FM, Ginsberg RJ, Cooper JD, *et al.* Open window thoracostomy in the management of postpneumonectomy empyema with or without bronchopleural fistula. *J Thorac Cardiovasc Surg* 1983; 86: 818–822.
20. Wain JC. Management of late postpneumonectomy empyema and bronchopleural fistula. *Chest Surg Clin N Am* 1996; 6: 529–541.
21. Abbas Ael-S, Deschamps C. Postpneumonectomy empyema. *Curr Opin Pulm Med* 2002; 8: 327–333.
22. Gharagozloo F, Margolis M, Facktor M, *et al.* Postpneumonectomy and postlobectomy empyema. *Thorac Surg Clin* 2006; 16: 215–222.
23. Misthos P, Kakaris S, Sepsas E, *et al.* Surgical management of late postpneumonectomy bronchopleural fistula: the transsternal, transpericardial route. *Respiration* 2006; 73: 525–528.
24. Frytak S, Lee RE, Pairolero PC, *et al.* Necrotic lung and bronchopleural fistula as complications of therapy in lung cancer. *Cancer Invest* 1988; 6: 139–143.
25. Sonobe M, Nakagawa M, Ichinose M, *et al.* Analysis of risk factors in bronchopleural fistula after pulmonary resection for primary lung cancer. *Eur J Cardiothorac Surg* 2000; 18: 519–523.
26. Arnold PG, Pairolero PC. Intrathoracic muscle flaps. An account of their use in the management of 100 consecutive patients. *Ann Surg* 1990; 211: 656–660.
27. Faber LP. Results of surgical treatment of stage III lung carcinoma with carinal proximity. *Surg Clin North Am* 1987; 67: 1001–1014.
28. Dartevelle PG, Khalife J, Chapelier A, *et al.* Tracheal sleeve pneumonectomy for bronchogenic carcinoma: report of 55 cases. *Ann Thorac Surg* 1988; 46: 68–72.
29. Dartevelle PG, Macchiarini P. Carinal resection for bronchogenic cancer. *Semin Thorac Cardiovasc Surg* 1996; 8: 414–425.
30. Dartevelle PG, Macchiarini P. Techniques of pneumonectomy. Sleeve pneumonectomy. *Chest Surg Clin N Am* 1999; 9: 401–417.
31. Roviaro GC, Varoli F, Rebuffat C, *et al.* Tracheal sleeve pneumonectomy for bronchogenic carcinoma. *J Thorac Cardiovasc Surg* 1994; 107: 13–18.
32. Bernard A, Deschamps C, Allen MS, *et al.* Pneumonectomy for malignant disease: factors affecting early morbidity and mortality. *J Thorac Cardiovasc Surg* 2001; 121: 1076–1082.
33. Algar FJ, Alvarez A, Aranda JL, *et al.* Prediction of early bronchopleural fistula after pneumonectomy: a multivariate analysis. *Ann Thorac Surg* 2001; 72: 1662–1667.
34. Borri A, Leo F, Veronesi G, *et al.* Extended pneumonectomy for non-small cell lung cancer: morbidity, mortality, and long-term results. *J Thorac Cardiovasc Surg* 2007; 5: 1266–1272.
35. Leo F, Scanagatta P, Baglio P, *et al.* The risk of pneumonectomy over the age of 70. A case–control study. *Eur J Cardiothorac Surg* 2007; 31: 780–782.
36. Powell ES, Pearce AC, Cook D, *et al.* UK pneumonectomy outcome study (UKPOS): a prospective observational study of pneumonectomy outcome. *J Cardiothorac Surg* 2009; 4: 41.
37. Stolz A, Pafko P, Harustiak T, *et al.* Risk factor analysis for early mortality and morbidity following pneumonectomy for non-small cell lung cancer. *Bratisl Lek Listy* 2011; 112: 165–169.

38. Petrella F, Radice D, Borri A, *et al.* The impact of preoperative body mass index on respiratory complications after pneumonectomy for non-small-cell lung cancer. Results from a series of 154 consecutive standard pneumonectomies. *Eur J Cardiothorac Surg* 2011; 39: 738–744.
39. Blyth DF. Pneumonectomy for inflammatory lung disease. *Eur J Cardiothorac Surg* 2000; 18: 429–434.
40. Owen RM, Force SD, Pickens A, *et al.* Pneumonectomy for benign disease: analysis of the early and late outcomes. *Eur J Cardiothorac Surg* 2013; 43: 312–317.
41. Tsuchiya R, Goya T, Naruke T, *et al.* Resection of tracheal carina for lung cancer. Procedure, complications, and mortality. *J Thorac Cardiovasc Surg* 1990; 99: 779–787.
42. Mathisen DJ, Grillo HC. Carinal resection for bronchogenic carcinoma. *J Thorac Cardiovasc Surg* 1991; 102: 16–22.
43. Dartevelle PG, Macchiarini P, Chapelier AR. Tracheal sleeve pneumonectomy for bronchogenic carcinoma: report of 55 cases. Updated in 1995. *Ann Thorac Surg* 1995; 60: 1854–1855.
44. Roviaro G, Varoli F, Romanelli A, *et al.* Complications of tracheal sleeve pneumonectomy: personal experience and overview of the literature. *J Thorac Cardiovasc Surg* 2001; 121: 234–240.
45. Porhanov VA, Poliakov IS, Selvaschuk AP, *et al.* Indications and results of sleeve carinal resection. *Eur J Cardiothorac Surg* 2002; 22: 685–694.
46. Subotich D, Mandarich D, Giroux D, *et al.* Sleeve pneumonectomy for lung cancer – survival and complications (single-center experience with 42 patients). *Acta Chir Belg* 2007; 107: 515–522.
47. Clagett OT, Geraci JE. A procedure for the management of postpneumonectomy empyema. *J Thorac Cardiovasc Surg* 1963; 45: 141–145.
48. Stafford EG, Clagett OT. Postpneumonectomy empyema. Neomycin instillation and definitive closure. *J Thorac Cardiovasc Surg* 1972; 63: 771–775.
49. Pairolero PC, Arnold PG, Trastek VF, *et al.* Postpneumonectomy empyema. The role of intrathoracic muscle transposition. *J Thorac Cardiovasc Surg* 1990; 99: 958–966.
50. Zaheer S, Allen MS, Cassivi SD, *et al.* Postpneumonectomy empyema: results after the Clagett procedure. *Ann Thorac Surg* 2006; 82: 279–286.
51. Massera F, Robustellini M, Della Pona C, *et al.* Predictors of successful closure of open window thoracostomy for postpneumonectomy empyema. *Ann Thorac Surg* 2006; 82: 288–292.
52. Weissberg D. Empyema and bronchopleural fistula. Experience with open window thoracostomy. *Chest* 1982; 82: 447–450.
53. Regnard JF, Alifano M, Puyo P, *et al.* Open window thoracostomy followed by intrathoracic flap transposition in the treatment of empyema complicating pulmonary resection. *J Thorac Cardiovasc Surg* 2000; 120: 270–275.
54. Miller JI, Mansour KA, Nahai F, *et al.* Single-stage complete muscle flap closure of the postpneumonectomy empyema space: a new method and possible solution to a disturbing complication. *Ann Thorac Surg* 1984; 38: 227–231.
55. Postmus PE, Kerstjens JM, de Boer WJ, *et al.* Treatment of post pneumonectomy pleural empyema by open window thoracostomy. *Eur Respir J* 1989; 2: 853–855.
56. Garcia-Yuste M, Ramos G, Duque JL, *et al.* Open-window thoracostomy and thoracomyoplasty to manage chronic pleural empyema. *Ann Thorac Surg* 1998; 65: 818–822.
57. Yokomise H, Takahashi Y, Inui K, *et al.* Omentoplasty for postpneumonectomy bronchopleural fistulas. *Eur J Cardiothorac Surg* 1994; 8: 122–124.
58. Okumura Y, Takeda S, Asada H, *et al.* Surgical results for chronic empyema using omental pedicled flap: long-term follow-up study. *Ann Thorac Surg* 2005; 79: 1857–1861.
59. Torre M, Quaini E, Ravini M, *et al.* 1987: Endoscopic gluing of bronchopleural fistula. Updated in 1994. *Ann Thorac Surg* 1994; 58: 901–902.
60. Tsunezuka Y, Sato H, Tsukioka T, *et al.* A new instrument for endoscopic gluing for bronchopleural fistulae. *Ann Thorac Surg* 1999; 68: 1088–1089.
61. Azorin JF, Francisci MP, Tremblay B, *et al.* Closure of a postpneumonectomy main bronchus fistula using video-assisted mediastinal surgery. *Chest* 1996; 109: 1097–1098.
62. Topcuoglu MS, Kayhan C, Ulus T. Transsternal transpericardial approach for the repair of bronchopleural fistula with empyema. *Ann Thorac Surg* 2000; 69: 394–397.
63. Stamatis G, Martini G, Freitag L, *et al.* Transsternal transpericardial operations in the treatment of bronchopleural fistulas after pneumonectomy. *Eur J Cardiothorac Surg* 1996; 10: 83–86.
64. Knaepen P. Discussion. *In*: Ginsberg RJ, Pearson FG, Cooper JD, *et al.* Closure of chronic postpneumonectomy bronchopleural fistula using the transsternal transpericardial approach. Ann Thorac Surg 1989; 47: 234–235.
65. de la Rivière AB, Defauw JJ, Knaepen PJ, *et al.* Transsternal closure of bronchopleural fistula after pneumonectomy. *Ann Thorac Surg* 1997; 64: 954–957.
66. Porhanov V, Poliakov I, Kononenko V, *et al.* Surgical treatment of 'short stump' bronchial fistula. *Eur J Cardiothorac Surg* 2000; 17: 2–7.
67. Spaggiari L, Carbognani P, Solli P, *et al.* Video-assisted modified Abruzzini technique for bronchopleural fistula repair. *Ann Thorac Surg* 1998; 65: 1198–1200.
68. Schneiter D, Cassina P, Korom S, *et al.* Accelerated treatment for early and late postpneumonectomy empyema. *Ann Thorac Surg* 2001; 72: 1668–1672.
69. Hollaus PH, Lax F, El-Nashef BB, *et al.* Natural history of bronchopleural fistula after pneumonectomy; a review of 96 cases. *Ann Thorac Surg* 1997; 63: 1391–1396.

70. Gossot D, Stern JB, Galetta D, *et al.* Thoracoscopic management of postpneumonectomy empyema. *Ann Thorac Surg* 2004; 78: 273–276.
71. Bagan P, Boissier F, Berna P, *et al.* Postpneumonectomy empyema treated with a combination of antibiotic irrigation followed by videothoracoscopic debridement. *J Thorac Cardiovasc Surg* 2006; 132: 708–710.
72. Ernst M, Nies C. Die thoracoskopische Therapie des Pleuraempyems nach Pneumonektomie. [Thoracoscopic therapy of pleural empyema after pneumonectomy.] *Chirurg* 1999; 70: 1480–1483.
73. Jadczuk E. Postpneumonectomy empyema. *Eur J Cardiothorac Surg* 1998; 14: 123–126.
74. Gregoire R, Deslauriers J, Beaulieu M, *et al.* Thoracoplasty: its forgotten role in the management of nontuberculous postpneumonectomy empyema. *Can J Surg* 1987; 30: 343–345.
75. Barker WL. Thoracoplasty. *Chest Surg Clin N Am* 1994; 4: 593–615.
76. Horrigan TP, Snow NJ. Thoracoplasty: current application to the infected pleural space. *Ann Thorac Surg* 1990; 50: 695–699.
77. Cornet E, Dupon H, Lucas A, *et al.* Current place of thoracoplasty in the treatment of pulmonary tuberculosis. *Rev Tuberc Pneumol* 1960; 24: 1185–1188.
78. Icard P, Le Rochais JP, Rabut B, *et al.* Andrews thoracoplasty as a treatment of post-pneumonectomy empyema: experience in 23 cases. *Ann Thorac Surg* 1999; 68: 1159–1163.

ERM 61 September 2013
CME Credit Application Form

This book has been accredited by the European Board for Accreditation in Pneumology (EBAP) for 5 CME credits.

To receive CME credits, read this issue of the Monograph, indicate the correct responses to the educational questions and complete the requested information. To return your application, you can either:

> use this form and return it completed to ERS Publications Office, 442 Glossop Road, Sheffield, S10 2PX, UK; fax to +44-114-2665064; or e-mail to info@ersj.org.uk

> fill in the online form available on the table of contents for the issue at erm.ersjournals.com

Certificates will be e-mailed to the address filled in below. Please allow 4 weeks for processing.

Applicant personal details

ERS Membership No. : .....Date of Birth (DD/MM/YYYY): ..... (if known)

Family Name: ..... First Name: .....

Mailing Address: .....

.....

.....

Postal Code: ..... City: ..... Country: .....

Telephone: +..... E-mail: .....

Educational questions

1. Which of the following are true? The incidence of post-operative pneumonia following major lung resection is:

❑ Somewhere under 40%. ❑ More than 50%. ❑ Increased in patients with COPD. ❑ Increased in patients with airway bacterial colonisation. ❑ Decreased in lung cancer patients.

2.Which of the following are true? Post-operative mortality following major lung resection:

❑ Can be as high as 60% when post-operative pneumonia occurs. ❑ Is about 70% in patients with empyema. ❑ Increases in patients requiring mechanical ventilation. ❑ Is unaffected by post-operative pneumonia in the long term. ❑ Is higher in patients with right-sided surgery.

3. Which of the following are true? Airway colonisation:

❑ Increases the risk of post-operative infection in most studies. ❑ Is mostly due to *Pseudomonas aeruginosa* and other Gram-negative bacilli. ❑ Can involve fungal species. ❑ Involves pathogens unrelated to those responsible for post-operative infectious complications. ❑ Increases the risk of bronchopleural fistula.

4. Which of the following is true? Antibiotic prophylaxis in patients undergoing lung resection:

❑ Decreases the risk of post-operative infections in most studies. ❑ Usually relies on third-generation cephalosporins or quinolones. ❑ Is more effective at preventing empyema than wound infection. ❑ Can be replaced by local antibiotics. ❑ Should last at least 3 days.

Continued on next page

5. Which of the following are true? Regarding the extent of lung resection:
❑ Pneumonectomy increases the risk of empyema in cases of wound infection. ❑ Empyema without bronchopleural fistula occurs more frequently after lobectomy than after pneumonectomy. ❑ Antibiotic prophylaxis to prevent empyema without fistula is likely to be more useful following pneumonectomy than following lobectomy. ❑ Expansion of the remaining lung parenchyma decreases the risk of empyema without fistula. ❑ The efficacy of prophylactic antibiotics has been clearly shown to differ between pneumonectomy and lobectomy patients.

6. What is the main adverse event related to the administration of bedaquiline?
❑ Nausea. ❑ Skin rash. ❑ Sepsis.

7. Which of the following is true? Pyrazinamide is:
❑ A bactericidal drug. ❑ A sterilising drug. ❑ Both a bactericidal and a sterilising drug.

8. Isoniazid should be prescribed to MDR-TB patients.
❑ True. ❑ False. ❑ It depends on the drug sensitivity testing results.

9. Which of the following statements is true?
❑ The lung is the organ most frequently infected by *Actinomyces*. ❑ Pulmonary actinomycosis predominantly occurs in females. ❑ *Actinomyces* are part of the normal flora of the human oropharynx. ❑ Only *Actinomyces israelii* is known to infect humans. ❑ Actinomycosis is a typical infection of immunocompromised patients.

10. Which antibiotic should not be used for the treatment of pulmonary actinomycosis?
❑ Amikacin. ❑ Penicillin. ❑ Erythromycin. ❑ Imipenem. ❑ Clindamycin.

11. Which of the following statements is true?
❑ Surgery is the preferred treatment for confirmed pulmonary actinomycosis complicated by broncholiths. ❑ For non-major haemoptysis due to pulmonary actinomycosis, a treatment trial with antibiotics should be undertaken. ❑ Pleural effusions complicating actinomycosis always require surgical drainage. ❑ The prognosis of thoracic actinomycosis complicated by chest wall swelling is very poor. ❑ In clinical practice, cultural confirmation of pulmonary actinomycosis is compulsory to establish the diagnosis.

12. A 50-year-old male presents with productive cough, fever and weight loss for 4 months. On image studies, a right-sided central lower lobe consolidation is detected. You consider actinomycosis as possible differential diagnosis. Which is the most appropriate next step?
❑ Prolonged treatment with penicillin under close follow-up. ❑ Bronchoscopy with biopsy sent to pathology and microbiology. ❑ Surgery to exclude malignancy and avoid possible complications like haemoptysis. ❑ Chest MRI to further narrow the possible differential diagnoses.

13. Which of the following statements is true? Sulphur granules:
❑ Contain actinomycetes. ❑ Do not occur in infections other than actinomycosis. ❑ Cannot be visualised with the Gomori methenamine silver stain. ❑ Can always be found in tissue infected by actinomycetes.

14. Which of the following are the complications of a lung abscess?
❑ Haemorrhage. ❑ Empyema. ❑ Bronchopleural fistula. ❑ All the above.

15. What period is justified for medical treatment of a lung abscess?
❑ 1–2 weeks. ❑ 4–6 weeks. ❑ 2–4 weeks. ❑ None of the above.

16. Which surgical procedure is usually suggested for lung abscess?
❑ Pneumonectomy. ❑ Drainage. ❑ Lobectomy. ❑ Extrapleural pneumonectomy.

17. For which of the following are humans accidental intermediate hosts?
❑ All echinococcal species. ❑ *Echinococcus granulosus* only. ❑ *Echinococcus multilocularis*. ❑ Both *Echinococcus granulosus* and *Echinococcus multilocularis*, but not *Echinococcus vogeli* or *Echinococcus oligarthrus*.

18. *Echinococcus granulosus* is the most common type of hydatid cyst in:
❑ Brain. ❑ Liver. ❑ Lung. ❑ Thoracic wall.

19. Hydatid cyst rupture into the pleural space is not followed by:
❑ Chronic pulmonary abscess. ❑ Pneumothorax. ❑ Hydropneumothorax. ❑ Empyema.

20. Chemotherapy alone, with albendazol and mebendazol, is an alternative for patients with:
❑ Multiple, disseminated, cysts. ❑ Single intact cysts or relapses. ❑ Contra-indications for surgery. ❑ All of the above.

21. What is obligatory in the management of residual cavity after organ-sparing extirpation methods?
❑ Local treatment with various antiscolicidal agents. ❑ Closure by different techniques. ❑ Local treatment with various antiscolicidal agents and individual closure of all bronchial openings. ❑ Individual closure of all bronchial openings.

22. The principles of surgical treatment should be:
❑ Evacuation of the cyst with removal of the endocyst, and avoidance of contamination. ❑ Management of the residual cavity (parenchyma-preserving methods). ❑ Preservation of as much tissue as possible. ❑ All of the above.

23. Which of the following statements is false?
❑ Approximately 10% of patients with parapneumonic effusions will require surgical management of their empyema. ❑ Empyemas are more common in females, with a male:female ratio of approximately 1:2. ❑ Empyema is more common in both extremes of age (children and elderly people). ❑ Empyema is generally secondary to pneumonia in 60–70% of cases.

24. Which statement is true for the management of pleural empyema?
❑ Chest radiography is sufficient to evaluate the chronicity of empyema and detect its underlying cause. ❑ For early-stage empyema, antibiotics are sufficient. ❑ If adequate pleural drainage is achieved, a period of 5 days of antibiotics is recommended. ❑ In case of adhesions and loculations, it is generally recommended that a small catheter is inserted under ultrasound or CT scan.

25. Which statements are true for the management of pleural empyema?
❑ Antibiotics should be discontinued immediately after decortication by thoracoscopy or thoracotomy. ❑ Empyema stage II is generally treated by formal thoracotomy to avoid restriction. ❑ Fibrinolysis is an option for early-stage empyema, in patients who do not tolerate surgery. ❑ Smaller wire-guided chest tubes should be used, because they cause significantly less pain than larger tubes, with no difference in the clinical outcome for the management of complicated pleural effusions.

Continued on next page

26. Which statements are true for the surgical management of chronic empyema (stage III)?

❑ Organisation of the empyema stage III usually begins 2–3 weeks after the onset of infection.

❑ Open-window thoracostomy consists of the subperiostal removal of a varying number of rib segments associated with myoplasty, which allows space obliteration by bringing the chest wall to the lung.

❑ When the underlying lung cannot re-expand after decortication, an obliteration of the pleural space cavity is mandatory. ❑ The VATS approach is never indicated in cases of chronic empyema.

Other titles in the series

ERM 60 – The Spectrum of Bronchial Infection
Francesco Blasi and Marc Miravitlles

ERM 59 – COPD and Comorbidity
Klaus F. Rabe, Jadwiga A. Wedzicha and Emiel F.M. Wouters

ERM 58 – Tuberculosis
Christoph Lange and Giovanni Battista Migliori

ERM 57 – Pulmonary Hypertension
M.M. Hoeper and M. Humbert

ERM 56 – Paediatric Asthma
K-H. Carlsen and J. Gerritsen

ERM 55 – New Developments in Mechanical Ventilation
M. Ferrer and P. Pelosi

ERM 54 – Orphan Lung Diseases
J-F. Cordier

ERM 53 – Nosocomial and Ventilator-Associated Pneumonia
A. Torres and S. Ewig

ERM 52 – Bronchiectasis
R.A. Floto and C.S. Haworth

ERM 51 – Difficult-to-Treat Severe Asthma
K.F. Chung, E.H. Bel and S.E. Wenzel

ERM 50 – Sleep Apnoea
W.T. McNicholas and M.R. Bonsignore

ORDER INFORMATION

Monographs are individually priced.
Visit the European Respiratory Society bookshop
www.ersbookshop.com
For bulk purchases contact the Publications Office directly.
European Respiratory Society Publications Office,
442 Glossop Road, Sheffield, S10 2PX, UK.
Tel: 44 (0)114 267 2860; Fax: 44 (0)114 266 5064; E-mail: sales@ersj.org.uk

EUROPEAN RESPIRATORY *monograph*

Pleuropulmonary infections are among the major causes of morbidity and mortality worldwide. This issue of the *European Respiratory Monograph* considers pleuropulmonary infections from both medical and surgical angles. It features chapters written by well-known experts in the fields of respiratory medicine and thoracic surgery, with particular focus on antibiotic prophylaxis prior to thoracic surgical procedures, the medical and surgical treatment of tuberculosis, fungal infections, abscesses and empyema of the lung, bronchiectasis, hydatid disease, mediastinitis, post-operative infection and complications, and much more.

Print ISSN 1025-448x
Online ISSN 2075-6674
Print ISBN 978-1-84984-036-1
Online ISBN 978-1-84984-037-8

Number 61 September 2013
€40.00

ISBN 978-1-84984-036-1